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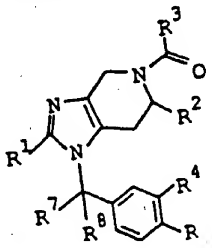
(54) 4,5,6,7-Tetrahydro-1H-imidazo 4,5-c pyridine-6-carboxylic acid amide derivatives as angiotensine II antagonistes.

(57) A compound of formula (I) :



(I)

or a pharmaceutically acceptable salt thereof ; wherein

R^1 represents
hydrogen,
halogen,
C_1-C_6 alkyl,
C_3-C_6 alkenyl,
C_3-C_6 alkynyl,
$R^{20}(CH_2)_n$- wherein R^{20} represents C_3-C_8 cycloalkyl, naphthyl, phenyl, or phenyl substituted with one to five of C_1-C_4 alkyl, halogen atom, trifluoromethyl, hydroxy, C_1-C_4 alkoxy, C_1-C_3 acyloxy, amino, N-mono-C_1-C_4 alkylamino, N-di-C_1-C_4 alkylamino, C_1-C_4 thioalkyl, C_1-C_3 alkylsulfonyl, nitro, and -$NHCOR^{21}$ wherein R^{21} represents C_1-C_3 alkyl, phenyl, C_1-C_3 alkylphenyl, aminophenyl, or C_1-C_4 alkylaminophenyl, and n is an integer of 1 to 6,
R^{20}-C(O)- wherein R^{20} is as defined above, or
R^{20}-CH(OH)- wherein R^{20} is as defined above ;

R^2 represents carbamoyl, mono- or di-C_1-C_6 alkylcarbamoyl, or 4- to 6-membered heterocyclic carbamoyl ;

R represents amino, carboxy, (1H-tetrazol-5-yl)phenyl, carboxyphenyl, carboxybenzamido, (1H-tetrazol-5-yl)benzamido, carboxyphenylcarbamoyl, or (1H-tetrazol-5-yl)-phenylcarbamoyl ;

R^3 represents -CH_2(phenyl), -CH(phenyl)$_2$, -CH(phenyl)CH_3, -CH(phenyl) (cyclohexyl), -CH_2CH_2(phenyl), -CH_2(C_1-C_6 alkoxyphenyl), or -CH_2(hydroxyphenyl) ; and

R^4, R^7, and R^8 each independently represents hydrogen or C_1-C_6 alkyl, is an angiotensin II antagonist.

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The present invention relates to 4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylic acid amide derivatives, intermediates for preparing the derivatives, and antagonists against angiotensin II (AII) comprising the derivatives.

Angiotensin II is an octapeptide hormone typically relating to hypertension, central nervous system diseases. It is therefore known that inhibition of the activities of angiotensin II is effective for the treatment of the hypertension and the central nervous system diseases.

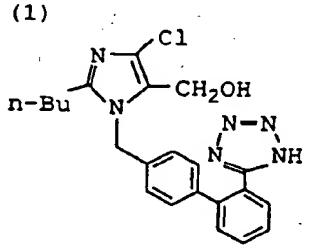
As angiotensin II inhibitors, there have been developed a renin inhibitor and an angiotensin-converting enzyme (ACE) inhibitor which inhibit the synthesis of angiotensin II. These inhibitors, however, have the problems that they are incapable of inhibiting the activities of angiotensin produced by other types of enzymes than renin and ACE, and that they may exert adverse effects to the other metabolic systems.

Angiotensin II acts through interaction with a specific receptor present in a cell membrane, so that an angiotensin II receptor antagonist which is capable of inhibiting all of the actions of the generated angiotensin II at the level of interaction with the receptor and gives no influence to the other metabolic systems has been desired as an antagonistic agent which is more specific and has less side effects.

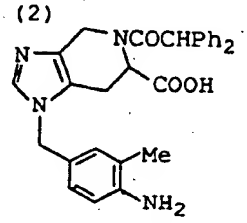
Some peptide analogs such as Saralasin have been reported as angiotensin II receptor antagonists, but they are unsatisfactory in their antagonistic activities and also the area of their applications is limited because of their lack of oral absorptivity.

Recently, non-peptidic angiotensin II receptor antagonists have been reported as the agents free of the said problems. Examples of these antagonists are DuP753, PD123177 (Bio-organic & Medical Chemistry Letters, 1(12), 711-716, 1991) and 4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylic acid derivatives disclosed in U.S. Patent No. 5,091,390, which are represented by the following structural formulae (1), (2), and (3), respectively:

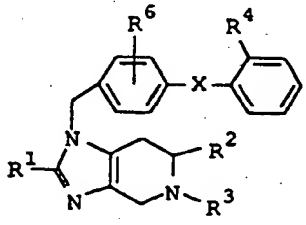
(1)



(2)



(3)



wherein, for example, R^1 is hydrogen, R^2 is CO_2H, R^3 is $COCH(Ph)_2$, X is NHCO, R^4 is CO_2H, and R^6 is CH_3.

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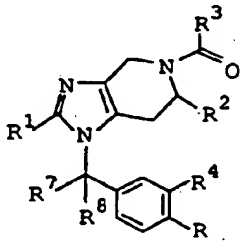
Nevertheless, request for the development of a compound having a higher specificity to the angiotensin II receptors and a higher antagonistic activity against angiotensin II is still rising.

In view of the above, the present inventors have extensive researches for wide range of compounds and, as a result, found that some specific 4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylic acid amide derivatives have a noticeably high antagonistic activity against angiotensin II and a high specificity to angiotensin II receptors as compared with the known compounds. Based on this finding, the present invention has been attained.

In a first aspect of the present invention, there is provided a compound of the formula (I):



(I)

or a pharmaceutically acceptable salt thereof; wherein

R^1 represents
hydrogen atom,
halogen atom,
C_1-C_6 alkyl,
C_3-C_6 alkenyl,
C_3-C_6 alkynyl,
$R^{20}(CH_2)_n$- wherein R^{20} represents C_3-C_8 cycloalkyl, naphthyl, phenyl, or phenyl substituted with one to five of C_1-C_4 alkyl, halogen atom, trifluoromethyl, hydroxy, C_1-C_4 alkoxy, C_1-C_3 acyloxy, amino, N-mono-C_1-C_4 alkylamino, N-di-C_1-C_4 alkylamino, C_1-C_4 thioalkyl, C_1-C_3 alkylsulfonyl, nitro, and -NHCOR^{21} wherein R^{21} represents C_1-C_3 alkyl, phenyl, C_1-C_3 alkylphenyl, aminophenyl, or C_1-C_4 alkylaminophenyl, and n is an integer of 1 to 6,
R^{20}-C(O)- wherein R^{20} is as defined above, or
R^{20}-CH(OH)- wherein R^{20} is as defined above;

R^2 represents carbamoyl, mono- or di-C_1-C_6 alkylcarbamoyl, or 4- to 6-membered heterocyclic carbamoyl;

R represents amino, carboxy, (1H-tetrazol-5-yl)phenyl, carboxyphenyl, carboxybenzamido, (1H-tetrazol-5-yl)benzamido, carboxyphenylcarbamoyl, or (1H-tetrazol-5-yl)-phenylcarbamoyl;

R^3 represents -CH_2(phenyl), -CH(phenyl)$_2$, -CH(phenyl)CH_3, -CH(phenyl) (cyclohexyl), -CH_2CH_2(phenyl), -CH_2(C_1-C_6 alkoxyphenyl), or -CH_2 (hydroxyphenyl); and

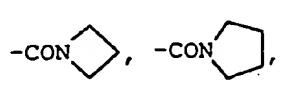
R^4, R^7, and R^8 each represent independently hydrogen atom or C_1-C_6 alkyl.

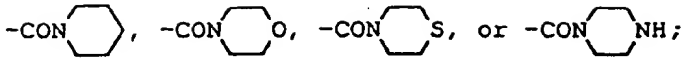
In a second aspect of the present invention, there are provided intermediates for producing the compound as defined in the first aspect of the present invention.

In a third aspect of the present invention, there is provided an angiotensin II antagonist comprising the compound as defined in the first aspect of the present invention.

The compound of the formula (I) or the pharmaceutically acceptable salt thereof have a noticeably high antagonistic activity against angiotensin II and a high specificity to angiotensin II receptors.

Preferred is a compound of the formula (I) or a pharmaceutically acceptable salt thereof wherein R^1 is hydrogen atom or C_1-C_6 alkyl group; R^2 is -$CONH_2$, -$CONHCH_3$, -$CON(CH_3)_2$, -$CONH(C_2H_5)$, -$CON(C_2H_5)_2$,

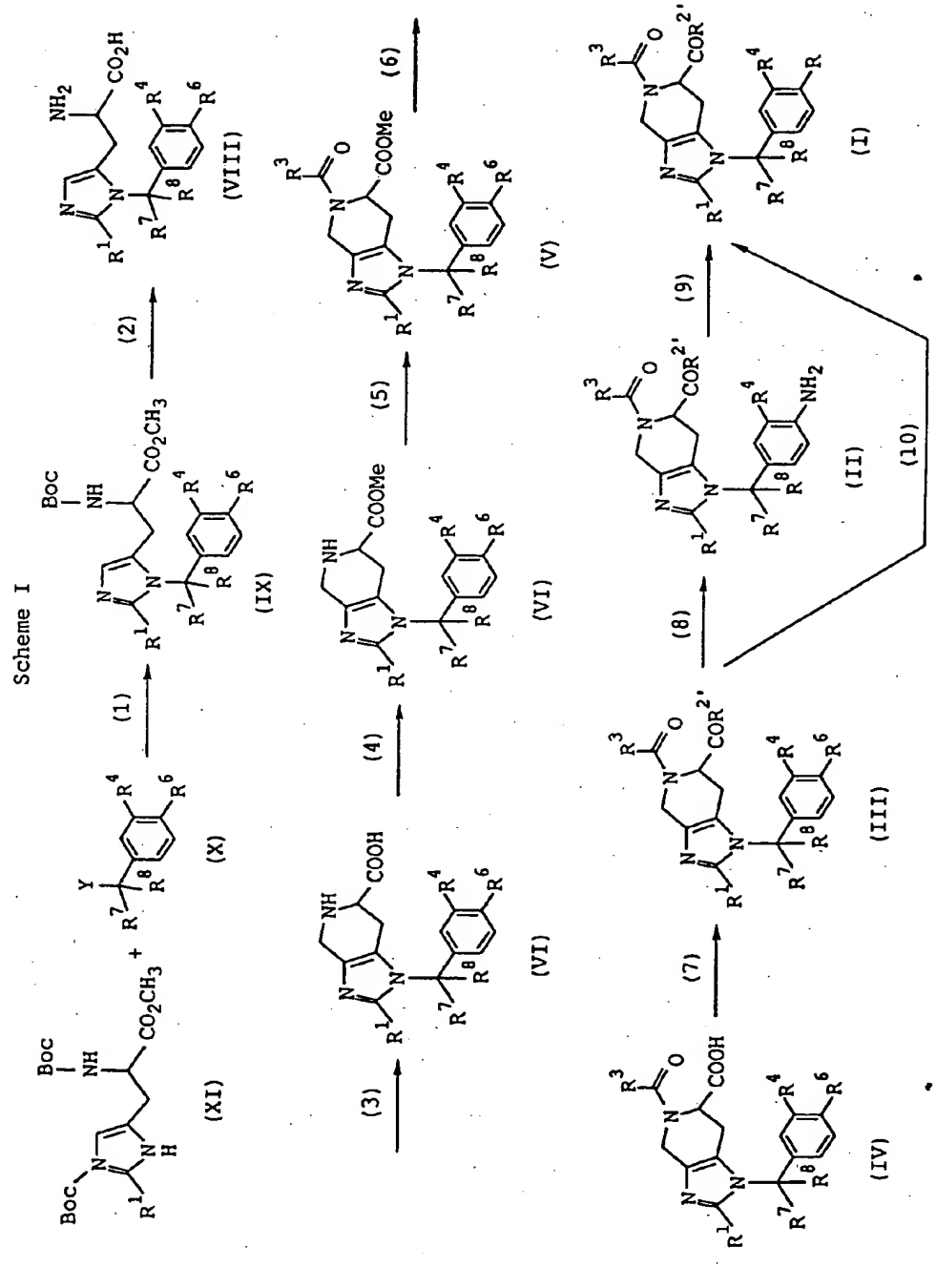




R is amino, carboxy, 2-(1H-tetrazol-5-yl)phenyl, 2-carboxyphenyl, 2-carboxybenzamido, 2-(1H-tetrazol-5-yl)benzamido, 2-carboxyphenylcarbamoyl, or 2-(1H-tetrazol-5-yl)phenylcarbamoyl; R^3 is -CH(phenyl)$_2$, -CH_2(phenyl), -CH(phenyl)CH_3, -CH(phenyl) (cyclohexyl), -CH_2CH_2(phenyl), -CH_2(p-methoxyphenyl), or -CH_2(p-hydroxyphenyl); and R^4, R^7, and R^8 each are independently hydrogen atom or C_1-C_2 alkyl.

The compound of the present invention has an asymmetric carbon atom at the 6-position of the condensed imidazole ring. Accordingly, the present invention includes any single stereoisomer thereof. Also, the present

Scheme I



With reference to Scheme I, the process A is described by dividing the process into ten steps (1)-(10).

Step (1)

A compound of the formula (XI) wherein R^1 is as defined above and Boc stands for tertiary butoxycarbonyl, is reacted with a compound of the formula (X) wherein Y is OH, Cl, Br, or OSO_2CF_3; R^4 is H or C_1-C_6 alkyl; R^6 is NO_2, cyanophenyl, cyano, (1H-tetrazol-5-yl)phenyl, or C_1-C_3 alkoxycarbonyl; and R^7 and R^8 each are independently H or C_1-C_6 alkyl, at 0 to 60°C for 10 to 48 hours to obtain a compound of the formula (IX) wherein R^1, R^4, R^6, R^7, R^8, and Boc are as defined above.

Step (2)

The compound of the formula (IX) obtained in the step (1) is treated with an acid, such as hydrochloric acid, to obtain a compound of the formula (VIII) wherein R^1, R^4, R^6, R^7, and R^8 are as defined above.

Step (3)

To the compound of the formula (VIII), there are added an acid and HCHO, and the mixture is reacted at 10 to 150°C for 0.5 to 4 hours to obtain a compound of the formula (VII) wherein R^1, R^4, R^6, R^7, and R^8 are as defined above.

Step (4)

The compound of the formula (VII) is suspended in an alcohol/trimethyl orthoformate mixture and then HCl is blown into the suspension to carry out reaction at 60 to 100°C for 4 to 8 hours to obtain a compound of the formula (VI) wherein R^1, R^4, R^6, R^7, and R^8 are as defined above.

Step (5)

The compound of the formula (VI) is added to a solution of acetonitrile, chloroform, dimethylformamide, or THF containing carbodiimide, 1-hydroxybenztriazole, diphenylacetic acid, or phenylcyclohexylacetic acid and reacted at 10 to 40°C for 10 to 48 hours to obtain a compound of the formula (V) wherein R^1, R^4, R^6, R^7, and R^8 are as defined above; and R^3 is -CH(phenyl)$_2$, -CH(phenyl)(cyclohexyl), -CH_2(phenyl), -CH_2CH_2(phenyl), -CH(phenyl)CH_3, -CH_2(C_1-C_6 alkoxyphenyl), or -CH_2(hydroxyphenyl).

Step (6)

An alkali, e.g. NaOH, is added to the compound of the formula (V) to obtain a compound of the formula (IV) wherein R^1, R^3, R^4, R^6, R^7, and R^8 are as defined above.

Step (7)

A nitrogen-containing compound is added to the compound of the formula (IV) and the mixture is reacted at 10 to 40°C for 10 to 24 hours to obtain a compound of the formula (III) wherein R^1, R^3, R^4, R^6, R^7, and R^8 are as defined above; and $R^{2'}$ is amino, mono- or di-C_1-C_6 alkylamino, or 4- to 6-membered heterocyclic amino.

When R^6 is (1H-tetrazol-5-yl)phenyl, it is obtained a compound of the formula (I) wherein R is (1H-tetrazol-5-yl)phenyl, in this step.

Step (8)

Tin chloride dihydrate is added to the compound of the formula (III) wherein R^6 is NO_2 and the mixture is reacted at 40 to 100°C for 10 to 120 minutes to obtain a compound of the formula (II) wherein R^1, $R^{2'}$, R^3, R^4, R^7, and R^8 are as defined above.

Step (9)

A benzoic acid derivative is reacted with the compound of the formula (II) at 10 to 40°C for 10 to 24 hours to obtain a compound of the formula (I) wherein R^1, $R^{2'}$, R^3, R^4, R^7, and R^8 are as defined above.

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Step (10)

When R_6 is cyanophenyl, there can be obtained a compound of the formula (I) wherein X is a C-C single bond, by hydrolyzing the compound of the formula (III).

A compound of the formula (XI) (raw material) can be obtained by the method described in J. Am. Chem. Soc., 114 (5), 1906-1908, 1992.

A compound of the formula (X) (raw material) can be obtained, for example, by the method described in J. Med. Chem., 33, 1312-1329, 1990, J. Med. Chem., 34, 2525-2547, 1991, J. Med. Chem., 34, 3248-3260, 1991, etc.

Conversion of substituents may be made by the conventional method available to one ordinarily skilled in the art.

Another example of a process for producing the compound of the present invention (hereinafter referred to as process B) is described in Scheme II.

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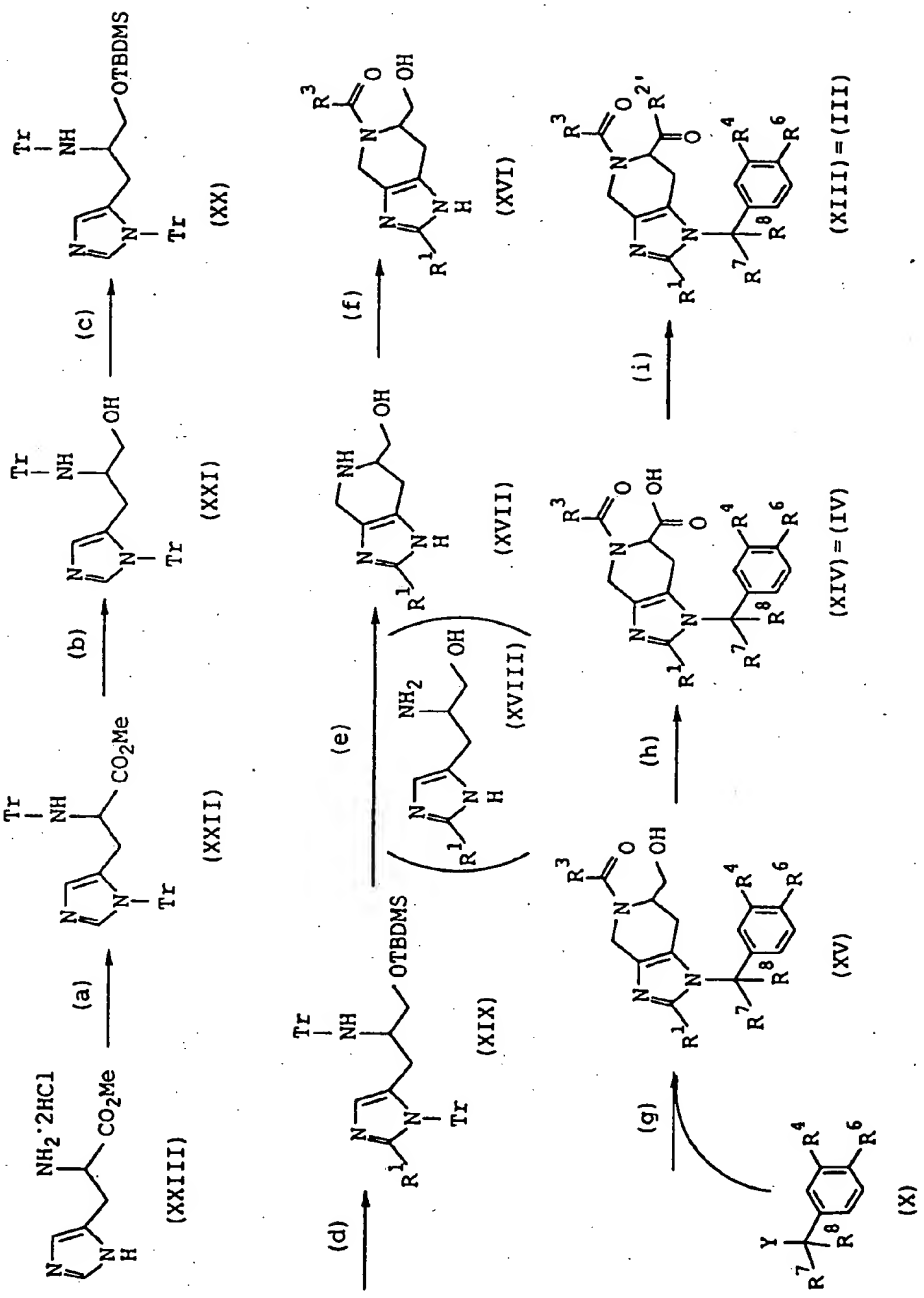
Scheme II


(a)
(b)
(c)
(d)
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(i)
(XXIII)
(XXII)
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(XIV) = (IV)
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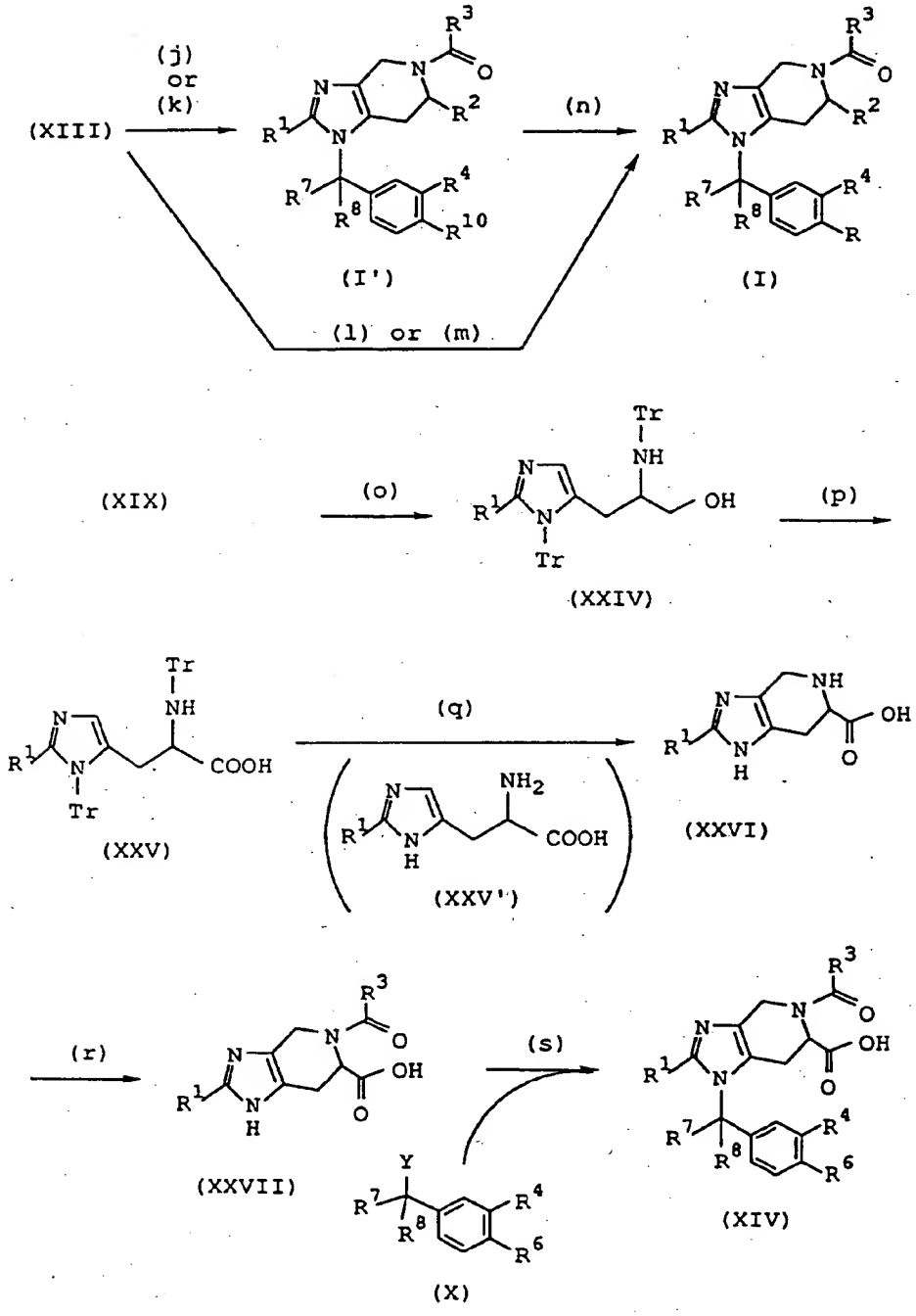

With reference to Scheme II the process B is described by dividing the process into 19 steps (a)-(s).

Step (a)

A compound of the formula (XXIII) is reacted with a tertiary amine such as Tr (triphenylmethyl) chloride and triethylamine in a solvent such as ether, THF (tetrahydrofuran), dioxane, methylene chloride, and chloroform at 10 to 60°C for 2 to 24 hours to obtain a compound of the formula (XXII). The compound of the formula (XXIII) is commercially available.

Step (b)

The compound of the formula (XXII) is reacted with a reducing agent such as lithium aluminum hydride in a solvent such as ether, THF, and dioxane at 0 to 40°C for 0.1 to 1 hour to obtain a compound of the formula (XXI).

Step (c)

The compound of the formula (XXI) is reacted with TBDMS (tertiary butyldimethylsilyl) chloride and imidazole in a solvent such as DMF (dimethylformamide) at 0 to 40°C for 0.5 to 6 hours to obtain a compound of the formula (XX) .

Step (d)

The compound of the formula (XX) is dissolved in a solvent such as ether, THF, and dioxane in an atmosphere of an inert gas such as nitrogen or argon gas, and reacted with a R^1 halide (chloride, bromide, or iodide) in the presence of a base such as butyl lithium (normal, secondary, or tertiary) and HMPA (hexamethylphosphoramide) at 0 to 40°C for 0.1 to 6 hours to obtain a compound of the formula (XIX).

Step (e)

An acid such as hydrochloric acid, is added to the compound of the formula (XIX) and the mixture is reacted at 10 to 120°C for 0.5 to 6 hours to obtain a compound of the formula (XVIII). This compound may be isolated. When it is not isolated, an aqueous HCHO solution is directly added thereto, and the mixture is reacted at 10 to 120 for 0.5 to 6 hours to obtain a compound of the formula (XVII).

Step (f)

The compound of the formula (XVII) is added to a solution of acetonitrile, chloroform, or THF containing carbodiimide, 1-hydroxybenztriazole, and R^3COOH, and reacted at 10 to 60°C for 1 to 48 hours to obtain a compound of the formula (XVI).

Step (g)

The compound of the formula (XVI) and a compound of the formula (X) are reacted in a solvent such as acetone, DMF, ether, THF, and chloroform in the presence of an appropriate base such as anhydrous potassium carbonate at 10 to 60°C for 1 to 48 hours to obtain a compound of the formula (XV).

Step (h)

The compound of the formula (XV) is reacted with an oxidizing agent such as chromic acid in a solvent such as acetone, methylene chloride, and chloroform at 10 to 40°C for 0.1 to 3 hours to obtain a compound of the formula (XIV).

Step (i)

The compound of the formula (XIV) is added to a solution of acetonitrile, chloroform, or THF containing carbodiimide, 1-hydroxybenztriazole, and linear or cyclic alkylamine, and reacted at 10 to 60°C for 1 to 48 hours to obtain a compound of the formula (XIII).

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Step (j)

When R^6 is methoxycarbonyl, an alkali such as a sodium hydroxide is added to a solution of the compound of the formula (XIV) in an alcohol, ether, THF, or a mixture thereof, and reacted at 10 to 40°C for 1 to 24 hours to obtain a compound of the formula (I') wherein R^{10} is carboxy.

Step (k)

When R^6 is nitro, tin chloride, or tin chloride dihydrate is added to a solution of the compound of the formula (XIII) in ethyl acetate, an alcohol, or a mixture thereof, and reacted in an atmosphere of an inert gas such as nitrogen or argon gas at 10 to 100°C for 0.1 to 1 hour to obtain a compound of the formula (I') wherein R^{10} is amino.

Step (l)

When R^6 is cyanophenyl, trimethyltin azide or tributyltin azide is added to a solution of the compound of the formula (XIII) in toluene or xylene, and the mixture is reacted in an atmosphere of an inert gas such as nitrogen or argon gas at 100 to 120°C for 12 to 120 hours, followed by a treatment with an acid such as hydrochloric acid to obtain a compound of the formula (I) wherein R^{10} is 1H-tetrazol-5-yl)phenyl.

Step (m)

When R^6 is ((1-triphenylmethyl)-1H-tetrazol-5-yl)phenyl, the compound of the formula (XIII) is dissolved in a solvent such as THF and dioxane, and an acid such as hydrochloric acid is added to the solution. Then, the mixture is reacted at 10 to 100°C for 0.1 to 6 hours to obtain a compound of the formula (I) wherein R^{10} is (1H-tetrazol-5-yl)phenyl.

Step (n)

When R^{10} is carboxy or amino, the compound of the formula (I') is dissolved in a solvent such as chloroform, acetonitrile, THF, and dioxane, and reacted by adding a compound having a required group at 10 to 60°C for 1 to 24 hours to obtain a compound of the formula (I).

Step (o)

The compound of the formula (XIX) is dissolved in a solvent such as THF and ether, and reacted with tetra-n-butylammonium fluoride at 0 to 40°C for 0.5 to 6 hours to obtain a compound of the formula (XXIV).

Step (p)

The compound of the formula (XXIV) is dissolved in DMF, and reacted with PDC (pyridinium dichromate) at 0 to 40°C for 0.5 to 24 hours to obtain a compound of the formula (XXV).

Step (q)

An acid such as hydrochloric acid is added to the compound of the formula (XXV) and the mixture is reacted at 10 to 120°C for 0.5 to 6 hours to obtain a compound of the formula (XXV'). This compound (XXV') may be isolated. When it is not isolated, an HCHO solution is directly added thereto and the mixture is reacted at 10 to 120°C for 0.5 to 6 hours to obtain a compound of the formula (XXVI).

Step (r)

The compound of the formula (XXVI) is added to a solution of acetonitrile, chloroform, or THF containing carbodiimide, dimethylformamide, 1-hydroxybenztriazole, and R^3COOH, and reacted at 10 to 60°C for 1 to 48 hours to obtain a compound of the formula (XXVII).

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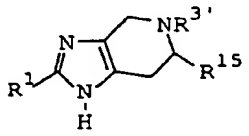
Step (s)

hydrogen atom,
halogen atom,
C_1-C_6 alkyl,
C_3-C_6 alkenyl,
C_3-C_6 alkynyl,
$R^{20}(CH_2)_n$- wherein R^{20} represents C_3-C_8 cycloalkyl, naphthyl, phenyl, or phenyl substituted with one to five of C_1-C_4 alkyl, halogen atom, trifluoromethyl, hydroxy, C_1-C_4 alkoxy, C_1-C_3 acyloxy, amino, N-mono-C_1-C_4 alkylamino, N-di-C_1-C_4 alkylamino, C_1-C_4 thioalkyl, C_1-C_3 alkylsulfonyl, nitro, and -$NHCOR^{21}$ wherein R^{21} represents C_1-C_3 alkyl, phenyl, C_1-C_3 alkylphenyl, aminophenyl, or C_1-C_4 alkylaminophenyl, and n is an integer of 1 to 6,
R^{20}-C(O)- wherein R^{20} is as defined above, or
R^{20}-CH(OH)- wherein R^{20} is as defined above;

R^{15} represents -CH_2-R^{17} wherein R^{17} represents hydroxy or t-butyldimethylsilyloxy, or -C(O)-R^{17} wherein R^{17} is as defined above; and

R^{16} represents hydrogen atom or triphenylmethyl;
with proviso that when R^1 and R^{16} are both hydrogen atom,
R^{15} is not -CH_2-OH, and that when R^1 is hydrogen atom or methyl and R^{16} is hydrogen atom, R^{15} is not -COOH.

(C) A compound of the formula (XXIX) :



(XXIX)

or a salt thereof; wherein

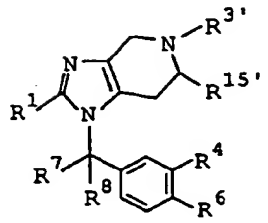
R^1 represents
hydrogen atom,
halogen atom,
C_1-C_6 alkyl,
C_3-C_6 alkenyl,
C_3-C_6 alkynyl,
$R^{20}(CH_2)_n$- wherein R^{20} represents C_3-C_8 cycloalkyl, naphthyl, phenyl, or phenyl substituted with one to five of C_1-C_4 alkyl, halogen atom, trifluoromethyl, hydroxy, C_1-C_4 alkoxy, C_1-C_3 acyloxy, amino, N-mono-C_1-C_4 alkylamino, N-di-C_1-C_4 alkylamino, C_1-C_4 thioalkyl, C_1-C_3 alkylsulfonyl, nitro, and -$NHCOR^{21}$ wherein R^{21} represents C_1-C_3 alkyl, phenyl, C_1-C_3 alkylphenyl, aminophenyl, or C_1-C_4 alkylaminophenyl, and n is an integer of 1 to 6,
R^{20}-C(O)- wherein R^{20} is as defined above, or
R^{20}-CH(OH)- wherein R^{20} is as defined above;

R^{15} represents -CH_2-R^{17} wherein R^{17} represents hydroxy or t-butyldimethylsilyloxy, or -C(O)-R^{17} wherein R^{17} is as defined above;

R^3 represents hydrogen atom, -$COCH_2$ (phenyl), -COCH(phenyl)$_2$, -COCH(phenyl)CH_3, -COCH(phenyl) (cyclohexyl), -$COCH_2CH_2$(phenyl), -$COCH_2$(C_1-C_6 alkoxyphenyl), or -$COCH_2$(hydroxyphenyl);
with proviso that when R^1 and $R^{3'}$ are both hydrogen atom,
R^{15} is not -COOH.

In the formula (XXIX), preferably R^1 is hydrogen atom or C_1-C_6 alkyl; R^{15} is -COOH; and $R^{3'}$ is -COCH(phenyl)$_2$ or -COCH(phenyl) (cyclohexyl).

(D) A compound of the formula (XXX) :



(XXX)

or a salt thereof; wherein

R^1 represents
hydrogen atom,
halogen atom,
C_1-C_6 alkyl,
C_3-C_6 alkenyl,
C_3-C_6 alkynyl,
$R^{20}(CH_2)_n$- wherein R^{20} represents C_3-C_8 cycloalkyl, naphthyl, phenyl, or phenyl substituted with one to five of C_1-C_4 alkyl, halogen atom, trifluoromethyl, hydroxy, C_1-C_4 alkoxy, C_1-C_3 acyloxy, amino, N-mono-C_1-C_4 alkylamino, N-di-C_1-C_4 alkylamino, C_1-C_4 thioalkyl, C_1-C_3 alkylsulfonyl, nitro, and -NHCOR^{21} wherein R^{21} represents C_1-C_3 alkyl, phenyl, C_1-C_3 alkylphenyl, aminophenyl, or C_1-C_4 alkylaminophenyl, and n is an integer of 1 to 6,
R^{20}-C(O)- wherein R^{20} is as defined above, or
R^{20}-CH(OH)- wherein R^{20} is as defined above;

$R^{3'}$ represents hydrogen atom, $-COCH_2$(phenyl), $-COCH(phenyl)_2$, $-COCH(phenyl)CH_3$, -COCH(phenyl) (cyclohexyl), $-COCH_2CH_2$(phenyl), $-COCH_2$(C_1-C_6 alkoxyphenyl), or $-COCH_2$(hydroxyphenyl);

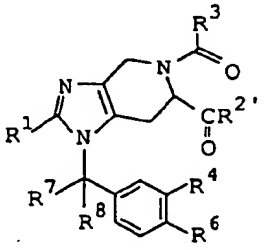
R^4, R^7, and R^8 each represent independently hydrogen atom or C_1-C_6 alkyl;

R^6 represents nitro, (1-triphenylmethyl-1H-tetrazol-5-yl)phenyl, cyano, C_1-C_3 alkoxycarbonyl, or cyanophenyl; and

R^{15} represents $-CH_2$-R^{19} wherein R^{19} represents hydrogen atom or C_1-C_6 alkyl group, or -C(O)-R^{19} wherein R^{19} is as defined above.

In the formula (XXX), preferably R^1 is hydrogen atom or C_1-C_6 alkyl; R^3 is $-COCH(phenyl)_2$ or -COCH(phenyl) (cyclohexyl); R^6 is nitro, 2-(1-triphenylmethyl-1H-tetrazol-5-yl)phenyl, cyano, methoxycarbonyl, or 2-cyanophenyl; R^4, R^7, and R^8 each are independently hydrogen atom or C_1-C_2 alkyl; and R^{19} is hydrogen atom or C_1-C_2 alkyl.

(E) A compound of the formula (XIII) :



(XIII)

or a salt thereof; wherein

R^1 represents
hydrogen atom,
halogen atom,
C_1-C_6 alkyl,
C_3-C_6 alkenyl,
C_3-C_6 alkynyl,
$R^{20}(CH_2)n$- wherein R^{20} represents C_3-C_8 cycloalkyl, naphthyl, phenyl, or phenyl sub-

stituted with one to five of C_1-C_4 alkyl, halogen atom, trifluoromethyl, hydroxy, C_1-C_4 alkoxy, C_1-C_3 acyloxy, amino, N-mono-C_1-C_4 alkylamino, N-di-C_1-C_4 alkylamino, C_1-C_4 thioalkyl, C_1-C_3 alkylsulfonyl, nitro, and -NHCOR^{21} wherein R^{21} represents C_1-C_3 alkyl, phenyl, C_1-C_3 alkylphenyl, aminophenyl, or C_1-C_4 alkylaminophenyl, and n is an integer of 1 to 6,

R^{20}-C(O)- wherein R^{20} is as defined above, or

R^{20}-CH(OH)- wherein R^{20} is as defined above;

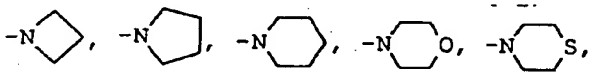
R$^{2'}$ represents amino, mono or di-C_1-C_6 alkylamino, or 4- to 6-membered heterocyclic amino;

R^3 represents -CH_2(phenyl), -CH(phenyl)$_2$, -CH(phenyl)CH_3, -CH(phenyl) (cyclohexyl), -CH_2CH_2(phenyl), -CH_2(C_1-C_6 alkoxyphenyl), or -CH_2(hydroxyphenyl);

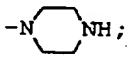
R^4, R^7 and R^8 each represent independently hydrogen atom or C_1-C_6 alkyl; and

R^6 represents nitro, (1-triphenylmethyl-1H-tetrazol-5-yl)phenyl, C_1-C_3 alkoxycarbonyl, cyano, or 2-cyanophenyl.

In the formula (XIII), preferably R^1 is hydrogen atom or C_1-C_6 alkyl; R^2 is -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -$NH(C_2H_5)$, $N(C_2H_5)_2$,



or



R^3 is -CH(phenyl)$_2$, or -CH(phenyl) (cyclohexyl); R^4, R^7, and R^8 each are independently hydrogen atom or C_1-C_2 alkyl; and R^6 is nitro, 2-(1-triphenylmethyl-1H-tetrazol-5-yl)phenyl, methoxycarbonyl, cyano, or 2-cyanophenyl.

The intermediate compounds of the present invention each have an asymmetric carbon atom at the 6-position of the condensed imidazole ring or the corresponding position. These intermediate compounds, therefore, include the single stereoisomer thereof. Also, the present invention includes a mixture of stereoisomers. In the present invention, these intermediate compounds are preferably the stereoisomers in which the 6-position of the condensed imidazole ring or the corresponding position is S configuration.

The salts of the above intermediate compounds can be obtained by using an acid or a base which is capable of chemically forming a salt with the intermediate compounds.

The formula (XIII') of (A) includes the formulae (IX) and (VIII) in the process A described above, and the formula (XXVIII) of (B) includes the formulae (XVIII), (XIX), (XXIV), (XXV), and (XXIII) in the process B described above. Also, the formula (XXIX) of (C) includes the formulae (XVII), (XVI), (XXVI), and (XXVII) in the process B, and the formula (XXX) of (D) includes the formulae (VII), (VI), (V), and (IV) in the process B. Therefore, these intermediate compounds (A) to (E) can be produced according to the process A or B.

The present invention further provides an angiotensin II antagonist comprising a compound of the formula (I) or a pharmaceutically acceptable salt thereof.

EXAMPLES

In the following, the present invention will be described with reference to the examples thereof. It is to be understood, however, that these examples are merely intended to be illustrative and not to be construed as limiting the scope of the invention.

Abbreviations used herein are as follows: cyc, cyclic; c-Hex, cyclohexyl; Ph, phenyl; Me, methyl; Et, ethyl; iPr, i-propyl; nPr, n-propyl; nBu, n-butyl; nHex, n-hexyl; Tr, triphenylmethyl.

Example 1: Process A, Step (1)

Synthesis of 3-(3-methyl-4-nitrophenyl)methyl-N-t-butoxycarbonyl-L-histidine methyl ester (IX-2)

Trifluoromethanesulfonic anhydride (10.00 g, 0.0354 mol) and dry methylene chloride (60 ml) were placed into a 500 ml separable flask having its interior atmosphere replaced with well dried nitrogen gas, and cooled to -70°C. Then a solution of 3-methyl-4-nitrobenzyl alcohol (5.34 g, 0.0325 mol) and N,N-diisopropylethylamine (6.2 ml, 0.0356 mol) in dry methylene chloride (40 ml) was added dropwise over a period of 15 minutes, followed by stirring for 30 minutes, after which a solution of N,1-bis-t-butoxycarbonyl-L-histidine methyl ester (XI-2) (10.00 g, 0.0271 mol) in dry methylene chloride (40 ml) was further added dropwise over a period of 20 minutes. Thereafter, the reaction flask was taken out of the cooling bath and the mixture was stirred at room temperature for 6 hours. The reaction mixture during rapid stirring was poured into a 0.2 M phosphate buffer solution (about 400 ml) to separate the methylene chloride layer, and the residue was washed with a 0.2 M phosphate buffer solution (about 400 ml), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to obtain an orange-colored oily material (12.07 g). This crude oily material was purified by silica gel column chromatography (LiChroprep Si60, 300 g, chloroform/methanol = 30/1) to obtain the objective compound (IX-2) (4.45 g; yield: 39.3%) as a light-yellow oily material.

There were similarly synthesized the corresponding compounds by using the raw compounds of the formulae (XI) and (X) wherein R^1 was H, Et, iPr, nBu, or nHex, and R^4, R^6, R^7, R^8, and Y were as shown in Table 1 below.

Table 1

Compound No.	R^4	R^6	R^7	R^8	Y
X-1	H	NO_2	H	H	OH
X-2	Me	NO_2	H	H	OH
X-3	H	2-CN-Ph	H	H	OH
X-4	H	2-CN-Ph	H	H	Br
X-5	Me	2-CN-Ph	H	H	Br
X-6	H	2-CN-Ph	H	H	OSO_2CF_3
X-7	Me	NO_2	Me	Me	OH
X-8	Me	2-CN-Ph	Me	Me	Br

Example 2: Process A, Step (2)

Synthesis of 3-(3-methyl-4-nitrophenyl)methyl-L-histidine dihydrochloride (VIII-2)

A 6 N hydrochloric acid solution (54.5 ml) was added to 3-(3-methyl-4-nitrophenyl)methyl-N-t-butoxycarbonyl-L-histidine methyl ester (IX-2) (1.3626 g, 0.00326 mol), and the mixture was refluxed under heating on a 120°C oil bath for 2.5 hours. The resulting solution was cooled and then concentrated to obtain the objective compound (VIII-2) (1.1406 g; yield: 92.9%) as a light-brown oily material.

Example 3: Process A, Step (3)

Synthesis of (S)-1-(3-methyl-4-nitrophenyl)methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylic acid dihydrochloride (VII-2)

A 1 N hydrochloric acid solution (13.7 ml) and a 37% formaldehyde solution (0.74 ml, 0.00907 mol) were added to 3-(3-methyl-4-nitrophenyl)methyl-L-histidine dihydrochloride (VIII-2) (1.1406 g, 0.00302 mol), and the mixture was stirred first at room temperature for half an hour and then on a 120°C oil bath for 1.5 hours. The mixture was then cooled and concentrated to obtain the objective compound (VII-2) (1.1538 g; yield: 98.0%) as yellowish brown crystals (decomposed at 256.5-258°C).

Example 4: Process A, Step (4)

Synthesis of (S)-1-(3-methyl-4-nitrophenyl)methyl-4,5, 6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylic acid methyl ester (VI-2)

(S)-1-(3-methyl-4-nitrophenyl)methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylic acid dihydrochloride (VII-2) (1.1538g, 0.00296 mol) was suspended in dry methanol (46 ml) and trimethylorthoformate (4.6 ml). Hydrogen chloride was blown into the suspension to saturation under ice cooling and stirring. The reaction solution was then stirred on a 90°C oil bath for 6 hours, cooled, and concentrated. The resulting yellowish brown oily material (0.7456 g) was purified by silica gel column chromatography (Kiesegel 60, 60 g, chloroform/methanol = 15/1) to obtain the objective compound (VI-2) (0.7076 g; yield: 72.3%) as an orange oily material.

Similarly to Examples 1-4, there were synthesized the compounds of Table 2.

Table 2

Compound No.	R^1	R^4	R^6	R^7	R^8
VI-1	H	H	NO_2	H	H
VI-2	H	Me	NO_2	H	H
VI-3	Et	Me	NO_2	H	H
VI-4	iPr	Me	NO_2	H	H
VI-5	nBu	Me	NO_2	H	H
VI-6	nHeX	Me	NO_2	H	H
VI-7	H	H	2-CN-Ph	H	H
VI-8	nBu	H	2-CN-Ph	H	H
VI-9	nBu	Me	2-CN-Ph	H	H
VI-10	nBu	Me	NO_2	Me	Me
VI-11	nBu	Me	2-CN-Ph	Me	Me

Example 5: Process A, Step (5)

Synthesis of (S)-5-diphenylacetyl-1-(3-methyl-4-nitrophenyl)methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]-pyridine-6-carboxylic acid methyl ester (V-2)

Acetonitrile (16 ml) was added to a mixture of N,N'-dicyclohexylcarbodiimide (DCCI) (2.1080 g, 0.01022 mol), 1-hydroxybenzotriazole (HBTA) (1.3806 g, 0.01022 mol), and diphenylacetic acid (2.1685 g, 0.01022 mol), followed by stirring at room temperature for 20 minutes. A solution of (S)-1-(3-methyl-4-nitrophenyl)methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylic acid methyl ester (VI-2) (2.7000 g, 0.00817 mol) in acetonitrile (14 ml) was added to the suspension, and the mixture was stirred at room temperature for 21 hours. An insoluble portion in the reaction mixture was filtered out and washed with acetonitrile, and then the filtrate and washings were joined and concentrated. The residue was dissolved in methylene chloride (40 ml), washed with a 10% sodium carbonate solution and a saturated brine, then dried over sodium sulfate and concentrated to obtain an orange oily material (4.5203 g). This crude oily material was purified by silica gel column chromatography (Kieselgel 60, 270 g, chloroform/methanol = 60/11) to obtain the objective compound (V-2) (2.8250 g; yield: 65.9%) as colorless crystals (mp: 174.5-177°C).

12:41:54

Example 6: Process A, Step (6)

Synthesis of (S)-5-diphenylacetyl-1-(3-methyl-4-nitrophenyl)methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]-pyridine-6-carboxylic acid (IV-2)

A 1 N sodium hydroxide solution (5.7 ml) was added to a solution of (S)-5-diphenylacetyl-1-(3-methyl-4-nitrophenyl)methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylic acid methyl ester (V-2) (2.8250 g, 0.00539 mol) in tetrahydrofuran/methanol (3/1, 17 ml), and the mixture was left at room temperature for 6 hours. The reaction mixture was concentrated, and the residue was weakly acidified by adding a 1 N hydrochloric acid solution (6.0 ml) and then extracted with methylene chloride. The methylene chloride layer was washed with a saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to obtain the objective compound (IV-2) (2.5558 g; yield: 93.0%) as a light-yellow viscous oily material. MS (EI) 492 (M-18).

The compounds of Table 3 were synthesized in the similar way to Examples 5 and 6.

Table 3

Compound No.	R^1	R^3	R^4	R^6	R^7	R^8
IV-1	H	$CH(Ph)_2$	H	NO_2	H	H
IV-2	H	$CH(Ph)_2$	Me	NO_2	H	H
IV-3	H	CH(Ph) ($cycC_6H_{11}$)	Me	NO_2	H	H
IV-4	Et	$CH(Ph)_2$	Me	NO_2	H	H
IV-5	iPr	$CH(Ph)_2$	Me	NO_2	H	H
IV-6	nBu	$CH(Ph)_2$	Me	NO_2	H	H
IV-7	nHeX	$CH(Ph)_2$	Me	NO_2	H	H
IV-8	H	$CH(Ph)_2$	H	2-CN-Ph	H	H
IV-9	nBu	$CH(Ph)_2$	H	2-CN-Ph	H	H
IV-10	nBu	$CH(Ph)_2$	Me	2-CN-Ph	H	H
IV-11	nBu	$CH(Ph)_2$	Me	NO_2	Me	Me
IV-12	nBu	$CH(Ph)_2$	Me	2-CN-Ph	Me	Me

Example 7: Process A, Step (7)

Synthesis of (S)-N,N-dimethyl-5-diphenylacetyl-1-(3-methyl-4-nitrophenyl)methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxamide (III-2)

Acetonitrile (40 ml) was added to a mixture of (S)-5-diphenylacetyl-1-(3-methyl-4-nitrophenyl)methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylic acid (IV-2) (2.5558 g, 0.00501 mol), DCCI (1.2916 g, 0.00626 mol) and HBTA (0.8456 g, 0.00626 mol), and the mixture was stirred at room temperature for 20 minutes. Dimethylamine hydrochloride (0.4488 g, 0.00626 mol) was added to the resulting suspension, and the mixture was stirred at room temperature for 18 hours. An insoluble portion in the reaction solution was filtered out and washed with acetonitrile. The filtrate and washings were joined and concentrated. The residue was dissolved in chloroform (40 ml), washed with a 10% sodium carbonate solution and a saturated brine, then dried over sodium sulfate, and concentrated to obtain a light-yellow oily material (4.3025 g). This crude oily material was purified by silica gel column chromatography (Kieselgel 60, 220 g, chloroform/methanol = 60/1) to obtain the objective compound (III-2) (2.3636 g; yield: 87.8%) as a light-yellow viscous oily material. MS (EI): 538 (M+1).

There were similarly synthesized the compounds of Table 4.

12:41:54

Table 4

Compound No.	R^1	$R^{2'}$	R^3	R^4	R^6	R^7	R^8
III-1	H	NMe_2	$CH(Ph)_2$	H	NO_2	H	H
III-2	H	NMe_2	$CH(Ph)_2$	Me	NO_2	H	H
III-3	H	NEt_2	$CH(Ph)_2$	Me	NO_2	H	H
III-4	H	NMe_2	CH(Ph) (cyc C_6H_{11})	Me	NO_2	H	H
III-5	H	cycNC_4H_8	$CH(Ph)_2$	Me	NO_2	H	H
III-6	H	cycNC_5H_{10}	$CH(Ph)_2$	Me	NO_2	H	H
III-7	H	cycNC_4H_8O	$CH(Ph)_2$	Me	NO_2	H	H
III-8	H	NH_2	$CH(Ph)_2$	H	NO_2	H	H
III-9	H	NHMe	$CH(Ph)_2$	H	NO_2	H	H
III-10	Et	NMe_2	$CH(Ph)_2$	Me	NO_2	H	H
III-11	iPr	NMe_2	$CH(Ph)_2$	Me	NO_2	H	H
III-12	nBu	NMe_2	$CH(Ph)_2$	Me	NO_2	H	H
III-13	nHeX	NMe_2	$CH(Ph)_2$	Me	NO_2	H	H
III-14	H	NMe_2	$CH(Ph)_2$	H	2-CN-Ph	H	H
III-15	nBu	NMe_2	$CH(Ph)_2$	H	2-CN-Ph	H	H
III-16	nBu	NMe_2	$CH(Ph)_2$	Me	2-CN-Ph	H	H
III-17	nBu	NMe_2	$CH(Ph)_2$	Me	NO_2	Me	Me
III-18	nBu	NMe_2	$CH(Ph)_2$	Me	2-CN-Ph	Me	Me

Example 8: Process A, Step (8)

Synthesis of (S)-1-(4-amino-3-methylphenyl)methyl-N,N-dimethyl-5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxamide (II-2)

(S)-N,N-dimethyl-5-diphenylacetyl-1-(3-methyl-4-nitrophenyl)methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]-pyridine-6-carboxamide (III-2) (2.3636 g, 0.00440 mol) was dissolved in a mixture of 28 ml of ethyl acetate and 5 ml of methanol, followed by addition of tin chloride dihydrate (4.9580 g, 0.0220 mol) and agitation of the solution on an 80°C oil bath in a stream of nitrogen for 30 minutes. The reaction mixture was cooled, neutralized by adding a 5% sodium carbonate solution, and concentrated. The residue was extracted with chloroform. The chloroform layer was washed with water, dried over sodium sulfate, and then concentrated to obtain a light-yellow foamy material (2.2368 g). This material was purified by silica gel column chromatography (Kieselgel 60, 120 g, chloroform/methanol = 50/1) to obtain the objective compound (II-2) (2.0077 g; yield: 90.0%) as a white foamy material. MS (EI) : 508 (M+1) .

There were similarly synthesized the compounds of Table 5.

12:41:54

Table 5

Compound No.	R^1	R^2	R^3	R^4	R^7	R^8
II-1	H	NMe_2	$CH(Ph)_2$	H	H	H
II-2	H	NMe_2	$CH(Ph)_2$	Me	H	H
II-3	H	NEt_2	$CH(Ph)_2$	Me	H	H
II-4	H	NMe_2	CH(Ph) (cyc C_6H_{11})	Me	H	H
II-5	H	cycNC_4H_8	$CH(Ph)_2$	Me	H	H
II-6	H	cycNC_5H_{10}	$CH(Ph)_2$	Me	H	H
II-7	H	cycNC_4H_8O	$CH(Ph)_2$	Me	H	H
II-8	H	NH_2	$CH(Ph)_2$	H	H	H
II-9	H	NHMe	$CH(Ph)_2$	H	H	H
II-10	Et	NMe_2	$CH(Ph)_2$	Me	H	H
II-11	iPr	NMe_2	$CH(Ph)_2$	Me	H	H
II-12	nBu	NMe_2	$CH(Ph)_2$	Me	H	H
II-13	nHex	NMe_2	$CH(Ph)_2$	Me	H	H
II-14	nBu	NMe_2	$CH(Ph)_2$	Me	Me	Me

Example 9: Process A, Step (9)

Synthesis of (S)-1-(4-(2-carboxybenzoylamino)-3-methylphenyl)methyl-N,N-dimethyl-5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxamide (I-2)

A solution of phthalic acid (0.7223 g, 0.00435 mol) in ethyl acetate (10 ml) was added to a solution of (S)-1-(4-amino-3-methylphenyl)methyl-N,N-dimethyl-5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo-[4,5-c]pyridine-6-carboxamide (II-2) (2.0077 g, 0.00396 mol) in ethyl acetate (30 ml) with stirring at room temperature. The mixture was stirred at room temperature for 23 hours, followed by filtration of the reaction mixture. The resulting white solid was washed with ethyl acetate (about 20 ml) and dried to obtain the objective compound (I-2, Compound No. 2) (2.4107 g; yield: 93.0%). MS 637 (EI) : (M-18) .

There were similarly synthesized the compounds of Table 6.

12:41:54

Table 6

Compound No.	R^1	$R^{2'}$	R^3	R^4	R	R^7	R^8	MS (EI)
I-1	H	NMe_2	$CH(Ph)_2$	H	2-carboxy-benzamido	H	H	623 (M-18)
I-2	H	NMe_2	$CH(Ph)_2$	Me	2-carboxy-benzamido	H	H	637 (M-18)
I-3	H	NEt_2	$CH(Ph)_2$	Me	2-carboxy-benzamido	H	H	665 (M-18)
I-4	H	NMe_2	CH(Ph) (cyc C_6H_{11})	Me	2-carboxy-benzamido	H	H	643 (M-18)
I-5	H	cycNC_4H_8	$CH(Ph)_2$	Me	2-carboxy-benzamido	H	H	663 (M-18)
I-6	H	cycNC_5H_{10}	$CH(Ph)_2$	Me	2-carboxy-benzamido	H	H	677 (M-18)
I-7	H	cycNC_4H_8O	$CH(Ph)_2$	Me	2-carboxy-benzamido	H	H	679 (M-18)
I-8	H	NH_2	$CH(Ph)_2$	H	2-carboxy-benzamido	H	H	595 (M-18)
I-9	H	NHMe	$CH(Ph)_2$	H	2-carboxy-benzamido	H	H	609 (M-18)
I-10	Et	NMe_2	$CH(Ph)_2$	Me	2-carboxy-benzamido	H	H	665 (M-18)
I-11	iPr	NMe_2	$CH(Ph)_2$	Me	2-carboxy-benzamido	H	H	679 (M-18)
I-12	nBu	NMe_2	$CH(Ph)_2$	Me	2-carboxy-benzamido	H	H	693 (M-18)
I-13	nBu	NMe_2	$CH(Ph)_2$	Me	2-carboxy-benzamido	Me	Me	721 (M-18)
I-14	nHex	NMe_2	$CH(Ph)_2$	Me	2-carboxy-benzamido	H	H	721 (M-18)

The results of elementary analysis of the compounds of Table 6 are shown in Table 7.

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Table 7

Compound No.	Elementary analysis	Calcd. for (C, H, N) (%)			Found (C, H, N) (%)		
I-1	$C_{38}H_{35}N_5O_5$	71.12,	5.50,	10.91	71.01,	5.57,	10.90
I-2	$C_{39}H_{37}N_5O_5$	71.43,	5.69,	10.68	71.34,	5.73,	10.70
I-3	$C_{41}H_{41}N_5O_5$	72.02,	6.04,	10.24	71.93,	6.10,	10.22
I-4	$C_{39}H_{43}N_5O_5$	70.78,	6.55,	10.58	70.70,	6.62,	10.55
I-5	$C_{41}H_{39}N_5O_5$	72.23,	5.76,	10.27	72.11,	5.89,	10.25
I-6	$C_{42}H_{41}N_5O_5$	72.50,	5.94,	10.06	72.39,	6.01,	10.04
I-7	$C_{41}H_{39}N_5O_6$	70.57,	5.63,	10.04	70.45,	5.71,	10.06
I-8	$C_{38}H_{31}N_5O_5$	70.46,	5.09,	11.41	70.33,	5.20,	11.39
I-9	$C_{37}H_{33}N_5O_5$	70.80,	5.30,	11.16	70.70,	5.44,	11.15
I-10	$C_{41}H_{41}N_5O_5$	72.02,	6.04,	10.24	71.90,	6.15,	10.26
I-11	$C_{42}H_{43}N_5O_5$	72.29,	6.21,	10.03	72.15,	6.35,	10.06
I-12	$C_{43}H_{45}N_5O_5$	72.55,	6.37,	9.84	72.44,	6.48,	9.88
I-13	$C_{45}H_{49}N_5O_5$	73.05,	6.67,	9.46	72.94,	6.78,	9.45
I-14	$C_{45}H_{49}N_5O_6$	73.05,	6.67,	9.46	72.98,	6.77,	9.47

Example 10: Process A, Step (10)

Synthesis of (S)-1-((2'-carboxybiphenyl-4-yl)methyl)-N,N-dimethyl-5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxamide (I-15)

Ten ml of ethyl alcohol and 20 ml of a 1 N aqueous sodium hydroxide solution were added to (S)-1-((2'-cyanobiphenyl-4-yl)methyl)-N,N-dimethyl-5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo-[4,5-c]pyridine-6-carboxamide (III-14) (1.9550 g, 0.00337 mol), and the mixture was refluxed under heating for 3 hours, then neutralized with a 6 N hydrochloric acid solution, and concentrated. The residue was extracted with chloroform, washed with water, dried over sodium sulfate, and concentrated to obtain a light-yellow foamy material (2.1179 g). This material was purified by silica gel column chromatography (Kieselgel 60, 110 g, chloroform/methanol = 50/1) to obtain the objective product (I-15; Compound No. 15) (1.8756 g; yield: 92.9%) as a white foamy material. MS (EI) : 580 (M-18) .

The compounds of Table 8, including compounds wherein R is 2-(1H-tetrazol-5-yl)phenyl, were synthesized in the similar way. The results of elementary analysis of the compounds of Table 8 are shown in Table 9.

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Table 8

Compound No.	R^1	$R^{2'}$	R^3	R^4	R	R^7	R^8	MS (EI)
I-15	H	NMe_2	$CH(Ph)_2$	H	2-carboxy-phenyl	H	H	580 (M-18)
I-16	H	NMe_2	$CH(Ph)_2$	H	2-(1H-tetrazol-5-yl)phenyl	H	H	622 (M+)
I-17	nBu	NMe_2	$CH(Ph)_2$	H	2-carboxy-phenyl	H	H	636 (M-18)
I-18	nBu	NMe_2	$CH(Ph)_2$	H	2-(1H-tetrazol-5-yl)phenyl	H	H	678 (M+)
I-19	nBu	NMe_2	$CH(Ph)_2$	Me	2-(1H-tetrazol-5-yl)phenyl	H	H	692 (M+)
I-20	nBu	NMe_2	$CH(Ph)_2$	Me	2-(1H-tetrazol-5-yl)phenyl	Me	Me	720 (M+)

Table 9

Compound No.	Elementary analysis	Calcd. for (C, H, N) (%)	Found (C, H, N) (%)
I-15	$C_{37}H_{34}N_4O_4$	74.23, 5.72, 9.36	74.11, 5.80, 9.35
I-16	$C_{37}H_{34}N_8O_2$	71.36, 5.50, 17.99	71.30, 5.55, 17.97
I-17	$C_{41}H_{42}N_4O_4$	75.20, 6.46, 8.56	75.11, 6.50, 8.54
I-18	$C_{41}H_{42}N_8O_2$	72.54, 6.23, 16.51	72.49, 6.30, 16.48
I-19	$C_{42}H_{44}N_8O_2$	72.81, 6.40, 16.17	72.77, 6.49, 16.15
I-20	$C_{44}H_{48}N_8O_2$	73.31, 6.71, 15.54	73.26, 6.78, 15.50

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Example 11: Process B, Step (a)

Synthesis of (S)-2-triphenylmethylamino-3-(1-triphenylmethylimidazol-5-yl)propanoic acid methyl ester (XXII)

Triethylamine (145 ml, 1.038 mol) was added to a solution of the compound (XXIII) (50.25 g, 0.208 mol) and TrCl (138.90 g, 0.498 mol) in CH_2Cl_2 (500 ml) dropwise with stirring under ice cooling for 30 minutes, followed by 6-hour stirring at room temperature. The reaction mixture was poured into water and extracted with CH_2Cl_2. The organic layer was washed with a saturated NaCl aqueous solution, dried over Na_2SO_4, and concentrated to obtain a crude product (168.87 g) as a yellow oily material. This crude product was purified by silica gel column chromatography (hexane/acetone = 3/1) to obtain the objective compound (XXII) (119.934 g; yield: 88.4%) as a white foamy material.

^{1}H-NMR ($CDCl_3$) δ: 2.71 (d, 1H, J=10.5 Hz, NH), 2.78 (dd, 1H, J=6.9, 13.8 Hz), 2.96 (dd, 1H, J=6.9, 13.8 Hz), 3.05 (s, 3H), 3.66 (dt, 1H, J=6.9, 10.5 Hz), 6.62 (s, 1H), 7.11-7.15 (m, 9H), 7.18-7.21 (m, 6H), 7.26-7.32 (m, 9H), 7.36 (s, 1H), 7.43 (d-like, 6H, J=7.3 Hz).

IR (ν_{max}, KBr): 3480, 1748, 1509, 1455, 1163, 748, 705 cm^{-1}.

Example 12: Process B, Step (b)

Synthesis of (S)-2-triphenylmethylamino-3-(1-triphenylmethylimidazol-5-yl)propanol (XXI)

The compound (XXII) (58.917 g, 0.0901 mol) was added to a suspension of $LiAlH_4$ (6.839 g, 0.180 mol) in dry Et_2O (590 ml) over a period of 2.5 hours. The mixture was stirred under ice cooling for one hour, and then $Na_2SO_4 \cdot 10H_2O$ was added to the resulting solution to dispose of the excess $LiAlH_4$, followed by filtration with Celite 545. The filtrate was concentrated and the residue was diluted with $CHCl_3$, washed with a saturated NH_4Cl aqueous solution and a saturated NaCl aqueous solution, then dried over Na_2SO_4, and concentrated to obtain the objective compound (56.390 g; yield: 100%) as a white foamy material.

^{1}H-NMR ($CDCl_3$) δ: 1.90 (b, 1H, NH), 1.95 (dd, 1H, J=6.4, 14.7 Hz), 2.38 (dd, 1H, J=3.2, 14.7 Hz), 2.91 (b, 1H), 2.99 (dd, 1H, J=6.4, 11.5 Hz), 3.47 (dd, 1H, J=3.2, 11.5 Hz), 4.95 (b, 1H, OH), 6.29 (s, 1H), 7.09-7.20 (m, 15H), 7.26-7.33 (m, 10H), 7.48-7.49 (m, 6H) .

IR (ν_{max}, KBr): 3480, 1550, 1455, 1036, 746, 702 cm^{-1}.

Example 13: Process B, Step (c)

Synthesis of (S)-1-t-butyldimethylsilyloxy-2-triphenylmethylamino-3-(1-triphenylmethylimidazol-5-yl)propane (XX)

Imidazole (12.269 g, 0.180 mol) and tert-butyldimethylsilyl chloride (TBDMSCl) (20.37 g, 0.135 mol) were added to a solution of the compound (XXI) (56.390 g, 0.0901 mol) in dry DMF (560 ml) under ice cooling, and the mixture was stirred at room temperature for 3.5 hours. The reaction mixture was poured into water, extracted with Et_2O, washed with water and a saturated NaCl aqueous solution, then dried over Na_2SO_4, and concentrated to obtain a light-yellow foamy material (67.602 g). This crude product was purified by silica gel column chromatography (hexane/acetone = 5/1) to obtain the objective compound (XX) (58.770 g; yield: 88.1%) as a white foamy material.

^{1}H-NMR ($CDCl_3$) δ: -0.13 (s, 6H), 0.80 (s, 9H), 1.60 (b, 1H, NH), 2.19 (dd, 1H, J=7.6, 14.2 Hz), 2.57 (dd, 1H, J=4.1, 14.2 Hz), 2.73 (b, 1H), 2.89 (dd, 1H, J=6.0, 9.6 Hz), 3.27 (dd, 1H, J=4.1, 9.6 Hz), 5.35 (s, 2H), 6.38 (s, 1H), 7.12-7.35 (m, 25H), 7.56 (d-like, 6H, J=7.3 Hz) .

IR (ν_{max}, KBr): 3100, 2990, 2970, 2925, 2890, 1508, 1480, 1455, 1253, 1132, 1090, 1072, 1035, 900, 830, 770, 742, 700, 658, 636 cm^{-1}.

Example 14: Process B, Step (d)

Synthesis of (S)-1-t-butyldimethylsilyloxy-2-triphenylmethylamino-3-(2-n-butyl-1-triphenylmethylimidazol-5-yl) propane (XIX-3)

A 1.5 N nBuLi/hexane mixed solution (61.0 ml, 0.0914 mol) was added dropwise to a solution of the compound (XX) (22.557 g, 0.0305 mol) in dry Et_2O (340 ml) over a period of 15 minutes by using an injector. Three minutes thereafter, nBuI (5.2 ml, 0.0457 mol) and HMPA (38 ml) were added dropwise with an injector under the same conditions. After 20-minute stirring, the mixture was heated to room temperature and further stirred for 4 hours. The reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with a saturated NaCl solution, then dried over Na_2SO_4, and concentrated to obtain a yellow oily material (25.830 g; yield: 100% up). This material was purified by silica gel column chromatography (hexane /acetone

= 20/1) to obtain the objective compound (XIX-3) (10.710 g; yield: 44.1%) as a light-yellow foamy material.

^{1}H-NMR (CD_2Cl_2) δ: -0.136, -0.144 (each s, each 3H), 0.58 (t, 3H, J=7.3 Hz), 0.77 (s, 9H), 0.89 (sext, 2H, J=7.3 Hz), 1.01 (m, 1H), 1.12 (m, 1H), 1.78 (m, 2H), 1.98 (dd, 1H, J=6.7, 14.0 Hz), 2.43 (dd, 1H, J=4.8, 14.0 Hz), 2.57 (b, 1H, CH), 3.06 (dd, 1H, J=6.9, 9.6 Hz), 3.10 (b, 1H, NH), 3.28 (dd, 1H, J=4.4, 9.6 Hz), 6.19 (s, 1H), 7.06-7.54 (m, 30H).

IR (ν_{max}, KBr): 3500, 3000, 2975, 2905, 1510, 1459, 1408, 1260, 1160, 1093, 1075, 1038, 834, 775, 746, 702, 640 cm^{-1}.

There were similarly synthesized the compounds of Table 10.

Table 10

Compound No.	R^1	Elementary analysis	Calcd. for (C, H, N) (%)			Found (C, H, N) (%)			MS(EI)
XIX-1	nPr	$C_{53}H_{59}N_3OSi$	81.39,	7.60,	5.37	81.50,	7.48,	5.30	782(M$^+$)
XIX-2	iPr	$C_{53}H_{59}N_3OSi$	81.39,	7.60,	5.37	81.47,	7.52,	5.29	782(M$^+$)
XIX-3	nBu	$C_{54}H_{61}N_3OSi$	81.46,	7.72,	5.28	81.61,	7.69,	5.19	796(M$^+$)
XIX-4	nHex	$C_{56}H_{65}N_3OSi$	82.61,	8.05,	5.16	82.76,	7.98,	5.09	814(M$^+$)

Example 15: Process B, Step (e)

Synthesis of (S)-2-amino-3-(2-n-butyl-1H-imidazol-5-yl)propanol (XVIII-3) and (S)-2-n-butyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-methanol hydrochloride (XVII-3)

A 1 N HCl aqueous solution (140 ml) and a 37% HCHO aqueous solution (3.6 ml) were added to the compound (XIX-3) (11.745 g, 0.0148 mol) and the mixture was stirred first at room temperature for 40 minutes and then in a 120°C oil bath for 4 hours. The reaction mixture was cooled and the insoluble portion was filtered out, followed by washing with water. The aqueous layer was washed with Et_2O, then concentrated, and dried to obtain the objective compound (XVII-3) (4.0370 g; yield: 97.0%) as a yellow solid.

^{1}H-NMR (D_2O) δ: 0.95 (t, 3H, J=7.3 Hz), 1.40 (sext, 2H, J=7.3 Hz), 1.79 (quint, 2H, J=7.3 Hz), 3.02 (t, 2H, J=7.3 Hz), 3.12 (d-like, 1H, J=4.6 Hz), 3.16 (bs, 1H), 3.85-3.90 (m, 2H), 4.08 (d-like, 1H, J=9.2 Hz), 4.48 (d, 1H, J=15.4 Hz), 4.52 (d, 1H, J=15.4 Hz).

IR(ν_{max}, KBr) : 3410, 2950, 1675, 1620, 1560, 1430, 1065 cm^{-1}.

The compounds shown in Table 11 were similarly synthesized.

Table 11

Compound No.	R_1	MS (EI)
XVII-1	nPr	195 (M-2HCl)
XVII-2	nHex	195 (M-2HCl)
XVII-3	nBu	209 (M-2HCl)
XVII-4	nHex	237 (M-2HCl)

By using the compound (XIX-3) (1.7750 g, 0.00223 mol) and an 1 N HCl aqueous solution (18 ml), the above reaction procedure was followed without adding the 37% HCHO aqueous solution to obtain the objective compound (XVIII-3) (0.7003 g; yield: 99.6%) as a yellow viscous material.

^{1}H-NMR (D_2O) δ: 0.96 (t, 3H, J=7.3 Hz), 1.39 (sext, 2H, J=7.3 Hz), 1.80 (quint, 2H, J=7.3 Hz), 3.00 (t, 2H, J=7.3 Hz), 2.8-3.3 (m, 3H), 3.7-4.3 (m, 2H), 6.05 (bs, 1H) .

MASS (EI) : 197 (M-2HCl) .

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There were similarly synthesized the compounds shown in Table 12.

Table 12

Compound No.	R^1	MASS (EI)
XVIII-1	nPr	183 (M-2HCl)
XVIII-2	iPr	183 (M-2HCl)
XVIII-3	nBu	197 (M-2HCl)
XVIII-4	nHex	225 (M-2HCl)

Example 16: Process B, Step (f)

Synthesis of (S)-2-n-butyl-5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-methanol (XVI-4)

Diphenylacetic acid (14.6617 g, 0.069 mol), N,N'-dicyclohexylcarbodiimide (DCCI) (14.2528 g, 0.069 mol), and 1-hydroxybenzotriazole (HBTA) (9.3345 g, 0.069 mol) were dissolved in dry THF (61 ml) and stirred at room temperature for 20 minutes. A solution of the compound (XVII-3) (6.0920 g, 0.0216 mol) in dry THF (30 ml) and dry triethylamine (TEA) (6.0 ml, 0.043 mol) were added to this solution, followed by stirring at room temperature for 14 hours. The insoluble portion was filtered out and washed with THF. The filtrate and washings were joined and concentrated to obtain a crude oily material (11.0015 g). This material was dissolved in a 1/1 mixture (100 ml) of THF and MeOH, after addition of a 1 N HCl aqueous solution (25 ml), left as it was for 8 hours. Then, to the mixture added a 1/1 mixture (100 ml) of THF and MeOH and a 1 N NaOH solution (50 ml), and the mixture was left as it was for 10 hours. The reaction mixture was concentrated. White crystals were precipitated by addition of H_2O (50 ml). These crystals were washed with water and then vacuum dried to give the compound (XVI-4) (2.1518 g; m.p. 199-202°C; yield: 24.7%).

^{1}H-NMR ($CDCl_3$) δ: 0.90, 0.91 (each t, 3H, J=7.3 Hz), 1.30-1.38 (m, 2H), 1.40-1.90 (b, 1H, OH), 1.55-1.70 (m, 2H), 2.55-2.62 (m, 2H), 2.33, 2.81 (s-like, dd, 2H), 3.43-3.58 (m, 2H), 3.86-4.08 (each d, 1H, J=16.7, 15.4 Hz), 4.47, 4.70 (bs, d, 2H, J=16.7 Hz), 5.28, 5.32, 5.51 (d, s, s, 2H, J=16.7 Hz), 7.10-7.60 (m, 10H), 8.80 (b, 1H, NH).

IR (ν_{max},KBr): 3425, 2970, 2930, 2860, 1620, 1450, 1420, 740, 695 cm^{-1}.

The compounds shown in Table 13 were similarly synthesized.

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Table 13

ıtary ysis	Calcd. for (C, H, N) (%)	Found (C, H, N) (%)	MS(EI)
N_3O_2	72.76, 6.09, 12.09	72.78, 5.89, 12.00	347(M^+)
N_3O_2	74.01, 6.99, 10.79	74.16, 6.83, 10.70	389(M^+)
N_3O_2	74.01, 6.99, 10.79	74.21, 6.90, 10.69	389(M^+)
N_3O_2	74.41, 7.24, 10.41	74.57, 7.20, 10.30	404(M^+)
N_3O_2	73.31, 8.61, 10.26	73.49, 8.55, 10.19	410(M^+)
N_3O_2	75.14, 7.71, 9.74	75.30, 7.68, 9.67	432(M^+)

Example 17: Process B, Step (g)

Synthesis of (S)-2-n-butyl-1-[(4-methoxycarbonylphenyl)methyl]-5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-methanol (XV-8)

Methyl 4-(bromomethyl)benzoate (0.0334 g, 0.00015 mol) and K_2CO_3 (0.0201 g, 0.00015 mol) were added to a solution of the compound (XVI-4) (0.0491 g, 0.00012 mol) in dry DMF (0.49 ml), and the mixture was stirred vigorously at room temperature for 24 hours. The reaction mixture was poured into water, extracted with EtOAc, washed with water, then dried over Na_2SO_4, and concentrated to obtain a light-yellow oily material (0.0656 g). This crude oily product was purified by silica gel column chromatography (hexane/ acetone = 1/2) to obtain the objective compound (XV-8) (0.0211 g), its 3-position isomer (0.0262 g), and a mixture of them (0.0035 g), each as a white foamy material (yield: 75.7%). The structures of the two compounds were determined by an NOE difference spectrum.

^{1}H-NMR ($CDCl_3$) δ: 0.86, 0.87 (each, t, 3H, J=7.3 Hz), 1.28-1.36 (m, 2H), 1.58-1.65 (m, 3H, $CH_3CH_2C\underline{H}_2CH_2$-, $CH_2O\underline{H}$), 1.99-2.63 (m, 2H), 2.52-2.63 (m, 2H), 3.31-3.57 (m, 2H, $C\underline{H}_2OH$), 3.92, 3.93 (each, s, 3H), 3.90, 4.13, 4.76, 5.42 (each, d, 2H, J=15.4 Hz), 4.40-4.47, 5.26-5.30 (each, m, 1H), 4.94, 5.02 (each, s, 2H), 5.35, 5.43 (each s, 1H), 6.91-6.99 (m, 2H), 7.17-7.32 (m, 10H), 7.98-8.01 (m, 2H).

IR (ν_{max},KBr): 3460, 1725, 1640, 1453, 1430, 1415, 1280, 1110, 743, 700 cm^{-1}.

Example 18: Process B, Step (g)

Synthesis of (S)-2-n-butyl-1-[(2'-cyanobiphenyl-4-yl) methyl]-5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo [4,5-c]pyridine-6-methanol (XV-10)

4'-(bromomethyl)-2-cyanobiphenyl (2.3655 g, 0.0869 mol) and K_2CO_3 (1.9222 g, 0.0139 mol) were added to a solution of the compound (XVI-4) (2.8060 g, 0.00695 mol) in dry DMF (28 ml), and the mixture was stirred vigorously at room temperature for 23 hours. The reaction mixture was poured into water, extracted with EtOAc, washed with water, dried over Na_2SO_4, and concentrated to obtained a light-yellow foamy material (4.5301 g). This material was purified by silica gel column chromatography to obtain the compound (XV-10) (0.9288 g), its 3-position isomer (1.4733 g), and a mixture of them (0.0207 g) (yield: 58.6%). The structures of the two compounds were determined by an NOE difference spectrum.

^{1}H-NMR ($CDCl_3$) δ: 0.89, 0.90 (each t, 3H, J=7.3 Hz), 1.36 (sext, 2H, J=7.3 Hz), 1.64-1.78 (m, 2H), 1.88 (bs, 1H, OH), 2.14, 2.72 (each dd, 1H, J=6.0, 15.6 Hz), 2.21, 2.51 (each d, 1H, J=15.6 Hz), 2.60-2.67 (m, 2H), 3.35-3.62 (m, 2H, $C\underline{H}_2OH$), 3.96, 4.93 (each d, 1H, J=17.0 Hz), 4.12, 4.78 (each d, 1H, J=15.6 Hz), 4.47-4.51, 5.35-5.40 (each m, 1H), 5.06-5.13 (m, 2H), 5.36, 5.42 (each s, 1H), 6.93-7.10 (m, 2H), 7.15-7.39 (m, 10H), 7.40-7.58 (m, 4H), 7.60-7.82 (m, 2H).

IR (ν_{max}, KBr): 3425, 2960, 2925, 2860, 1637, 1500, 1480, 1450, 1410, 1375, 760, 740, 700 cm^{-1}.

There were similarly synthesized the compounds shown in Table 14.

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Table 14

Compound No.	R^1	R^3	R^4	R^7	R^8	R^6	Elementary analysis	Calcd. for (C, H, N) (%)	Found (C, H, N) (%)	MS(EI)
XV-1	H	$(Ph)_2CH$	H	H	H	COOMe	$C_{30}H_{29}N_3O_4$	72.71, 5.90, 8.48	72.90, 5.79, 8.40	496(M^+)
XV-2	H	$(Ph)_2CH$	H	Me	Me	COOMe	$C_{32}H_{33}N_3O_4$	73.40, 6.35, 8.02	73.51, 6.30, 7.99	524(M^+)
XV-3	H	$(Ph)_2CH$	Me	H	H	NO_2	$C_{29}H_{28}N_4O_4$	70.15, 5.68, 11.28	70.30, 5.60, 11.22	497(M^+)
XV-4	H	$(Ph)_2CH$	H	H	H	2-CN-Ph	$C_{35}H_{30}N_4O_2$	78.04, 5.61, 10.40	78.20, 5.54, 10.33	539(M^+)
XV-5	H	$(Ph)_2CH$	H	H	H	2-(1-Tr-1H-tetrazol-5-yl)Ph	$C_{54}H_{45}N_7O_2$	78.71, 5.50, 11.90	78.89, 5.40, 11.83	824(M^+)
XV-6	nPr	$(Ph)_2CH$	H	H	H	2-CN-Ph	$C_{38}H_{36}N_4O_2$	78.59, 6.25, 9.65	78.71, 6.19, 9.58	581(M^+)
XV-7	iPr	$(Ph)_2CH$	H	H	H	2-CN-Ph	$C_{38}H_{36}N_4O_2$	78.59, 6.25, 9.65	78.66, 6.21, 9.63	581(M^+)
XV-8	nBu	$(Ph)_2CH$	H	H	H	COOMe	$C_{34}H_{37}N_3O_4$	74.02, 6.76, 7.62	74.21, 6.66, 7.59	552(M^+)
XV-9	nBu	$(Ph)_2CH$	Me	H	H	NO_2	$C_{34}H_{38}N_4O_4$	72.06, 6.76, 9.89	72.25, 6.64, 9.78	567(M^+)
XV-10	nBu	$(Ph)_2CH$	H	H	H	2-CN-Ph	$C_{39}H_{38}N_4O_2$	78.76, 6.44, 9.42	78.91, 6.38, 9.39	595(M^+)
XV-11	nBu	$(Ph)_2CH$	H	H	H	2-(1-Tr-1H-tetrazol-5-yl)Ph	$C_{58}H_{53}N_7O_2$	79.15, 6.07, 11.14	79.30, 5.98, 11.07	880(M^+)
XV-12	nBu	(Ph)(c-Hex)CH	H	H	H	2-CN-Ph	$C_{39}H_{44}N_4O_2$	77.97, 7.38, 9.33	78.10, 7.29, 9.30	601(M^+)
XV-13	nHex	$(Ph)_2CH$	H	H	H	2-CN-Ph	$C_{41}H_{42}N_4O_2$	79.07, 6.80, 9.00	79.22, 6.77, 8.95	623(M^+)

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Example 19: Process B, Step (h)

Synthesis of (S)-2-n-butyl-1-[(4-methoxycarbonylphenyl)methyl]-5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylic acid (XIV-8)

CrO_3 (0.33 g) was dissolved in H_2O (0.62 ml), and concentrated H_2SO_4 was slowly added dropwise thereto. The resultantly produced salt was dissolved in H_2O (0.1 ml) to prepare an oxidizing reagent. Meanwhile, the compound (XV-8) (0.2916 g) was dissolved in acetone (4.4 ml), and the previously prepared oxidizing reagent was added dropwise thereto at room temperature until the orangish red color did not fade away. After 30-minute stirring, iPrOH was added to the reaction mixture until it assumed a green color, and then the mixture was concentrated. The resulting crude product was purified by silica gel column chromatography ($CHCl_3$/MeOH = 8/1) to obtain the objective compound (XIV-8) (0.1883 g; m.p. 177-180°C ; yield: 63.0%).

^{1}H-NMR ($CDCl_3$) δ: 0.79, 0.83 (each t, 3H, J=7.3 Hz), 1.18-1.28 (m, 2H), 1.40-1.55 (m, 2H), 1.77, 2.99, 3.24-3.44 (m, d, m, 2H, J=14.7 Hz), 2.45-2.70 (m, 2H), 3.89, 3.92 (each s, 3H), 4.28, 4.57, 4.69, 5.07 (each d, 2H, J=14.7 Hz), 5.17-5.27 (m, 2H), 5.51, 5.55 (each s, 1H), 5.51-5.55, 5.70 (d, 1H, J=5.5 Hz), 7.09-7.45 (m, 12H), 7.90-8.10 (m, 2H).

IR (ν_{max}, KBr) : 3470, 2980, 1726, 1640, 1615, 1506, 1455, 1435, 1417, 1283, 1190, 1112, 750, 700 cm^{-1}.

Example 20: Process B, Step (h)

Synthesis of (S)-2-n-butyl-1-[(2'-cyanobiphenyl-4-yl) methyl]-5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo [4,5-c]pyridine-6-carboxylic acid (XIV-10)

The oxidizing reagent (0.9 ml) as prepared in Example 19 was added dropwise to a solution of the compound (XV-10) (0.6249 g, 0.00105 mol) in acetone (9.4 ml) at room temperature. After 30-minute stirring, iPrOH was added to the reaction mixture until it assumed a green color, and then the mixture was concentrated. The resulting crude product was purified by silica gel column chromatography ($CHCl_3$/MeOH = 6/1) to obtain the compound (XIV-10) (0.3619 g; yield: 56.6%) as a white foamy material.

^{1}H-NMR ($CDCl_3$) δ: 0.75-1.06 (m, 3H), 1.15-1.40 (m, 2H), 1.44-1.70 (m, 2H), 2.46-2.64 (m, 2H), 2.69, 2.93 (each dd, 1H, J=6.0, 15.6 Hz), 3.08, 3.31 (each d, 1H, J=15.6 Hz), 4.27, 4.67 (each d, 1H, J=15.6 Hz), 4.58, 4.99 (each d, 1H, J=15.6 Hz), 4.94-5.25 (m, 2H), 5.32, 5.43 (each s, 1H), 4.83, 5.68 (each d, 1H, J=6.0 Hz), 7.02-7.85 (m, 18H).

IR (ν_{max}, KBr) ν_{max}: 3425, 2960, 1620, 1500, 1408, 758, 742, 700, 630, 560 cm^{-1}.

There were similarly synthesized the compounds shown in Table 15.

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Table 15

Compound No.	R^1	R^3	R^4	R^7	R^8	R^6	Elementary analysis	Calcd. for (C, H, N) (%)	Found (C, H, N) (%)	MS(FAB)
XIV-1	H	$(Ph)_2CH$	H	H	H	COOMe	$C_{30}H_{27}N_3O_5$	70.71, 5.34, 8.25	70.89, 5.29, 8.18	510(M^+)
XIV-2	H	$(Ph)_2CH$	H	Me	Me	COOMe	$C_{32}H_{31}N_3O_5$	71.49, 5.81, 7.82	71.63, 5.77, 7.74	538(M^+)
XIV-3	H	$(Ph)_2CH$	Me	H	H	NO_2	$C_{29}H_{26}N_4O_5$	68.22, 5.13, 10.97	68.40, 5.09, 10.88	511(M^+)
XIV-4	H	$(Ph)_2CH$	H	H	H	2-CN-Ph	$C_{35}H_{28}N_4O_3$	76.07, 5.11, 10.14	76.21, 5.04, 10.07	553(M^+)
XIV-5	H	$(Ph)_2CH$	H	H	H	2-(1-Tr-1H-tetrazol-5-yl)Ph	$C_{54}H_{43}N_7O_3$	77.40, 5.17, 11.70	77.55, 5.09, 11.65	838(M^+)
XIV-6	nPr	$(Ph)_2CH$	H	H	H	2-CN-Ph	$C_{38}H_{34}N_4O_3$	76.75, 5.76, 9.42	76.91, 5.65, 9.38	595(M^+)
XIV-7	iPr	$(Ph)_2CH$	H	H	H	2-CN-Ph	$C_{38}H_{34}N_4O_3$	76.75, 5.76, 9.42	76.88, 5.59, 9.40	595(M^+)
XIV-8	nBu	$(Ph)_2CH$	H	H	H	COOMe	$C_{34}H_{35}N_3O_5$	72.19, 6.24, 7.43	72.30, 6.20, 7.38	566(M^+)
XIV-9	nBu	$(Ph)_2CH$	Me	H	H	NO_2	$C_{34}H_{36}N_4O_5$	70.33, 6.25, 9.65	70.50, 6.19, 9.62	581(M^+)
XIV-10	nBu	$(Ph)_2CH$	H	H	H	2-CN-Ph	$C_{39}H_{36}N_4O_3$	76.95, 5.96, 9.20	77.09, 5.88, 9.14	609(M^+)
XIV-11	nBu	$(Ph)_2CH$	H	H	H	2-(1-Tr-1H-tetrazol-5-yl)Ph	$C_{58}H_{51}N_7O_3$	77.92, 5.75, 10.97	80.10, 5.64, 10.85	894(M^+)
XIV-12	nBu	(Ph)(c-Hex)CH	H	H	H	2-CN-Ph	$C_{39}H_{42}N_4O_3$	76.19, 6.89, 9.11	76.33, 6.75, 9.08	615(M^+)
XIV-13	nHex	$(Ph)_2CH$	H	H	H	2-CN-Ph	$C_{41}H_{40}N_4O_3$	77.33, 6.33, 8.80	77.21, 6.54, 8.65	637(M^+)

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Example 21: Process B, Step (i)

Synthesis of 4-[[(S)-2-butyl-1-[(4-methoxycarbonylphenyl)methyl]-5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-6-yl]carbonyl]morpholine (XIII-8)

The compound (XIV-8) (0.1315 g, 0.00023 mol), DCCI (0.0624 g, 0.0003 mol), HBTA (0.0377 g, 0.00028 mol), and morpholine (0.024 ml, 0.00028 mol) were dissolved in dry THF (2.0 ml) and stirred at room temperature for 19 hours. The insoluble portion was filtered out and washed with THF. The filtrate and washings were joined and concentrated to obtain a crude oily product (0.3010 g). This crude product was purified by silica gel column chromatography ($CHCl_3$/MeOH = 60/1) to obtain a white foamy material (0.1204 g). This material was again purified by using a preparative TLC plate (0.5 mm thick, 20 cm x 20 cm; developing solvent: hexane/acetone = 2/3) to obtain the objective compound (XIII-8) (0.0911 g; yield: 61.7%) .

^{1}H-NMR ($CDCl_3$) δ: 0.84 (t, 3H, J=7.3 Hz), 1.28 (sext, 2H, J=7.3 Hz), 1.58 (quint, 2H, J=7.3 Hz), 2.49 (t, 2H, J=7.3 Hz), 2.70 (dd, 1H, J=6.0, 15.1 Hz), 2.80 (d, 1H, J=15.1 Hz), 3.25-3.70 (b, 8H), 3.92 (s, 3H), 4.26 (d, 1H, J=15.1 Hz), 4.90 (d, 1H, J=15.1 Hz), 5.02, 5.07 (each d, each 1H, J=17.4 Hz), 5.35 (s, 1H), 5.96 (d, 1H, J=6.0 Hz), 7.09 (d, 2H, J=8.3 Hz), 7.17-7.35 (m, 10H), 8.02 (d, 2H, J=8.3 Hz).

IR (ν_{max}, KBr): 3460, 1725, 1645, 1455, 1433, 1415, 1280, 1230, 1113, 750, 700 cm^{-1}.

Example 22: Process B, Step (i)

Synthesis of 4-[[(S)-2-butyl-1-[(2'-cyanobiphenyl-4-yl) methyl]-5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo-[4,5-c]pyridin-6-yl]carbonyl]morpholine (XIII-10)

The compound (XIV-10) (0.3301 g, 0.000542 mol), DCCI (0.1455 g, 0.000705 mol), HBTA (0.0953 g, 0.000705 mol), and morpholine (0.06 ml, 0.000705 mol) were dissolved in dry THF (5.0 ml) and stirred at room temperature for 48 hours. The insoluble portion was filtered out and washed with THF. The filtrate and washings were joined and concentrated to obtain a crude product (0.5500 g). This crude product was purified by silica gel column chromatography (hexane/acetone = 2/3) to obtain the objective compound (XIII-10) (0.1764 g; yield: 48.0%) as a white foamy material.

^{1}H-NMR ($CDCl_3$) δ: 0.87 (t, 3H, J=7.3 Hz), 1.32 (sext, 2H, J=7.3 Hz), 1.64 (quint, 2H, J=7.3 Hz), 2.55 (t, 2H, J=7.3 Hz), 2.77 (dd, 1H, J=6.0, 15.1 Hz), 2.86 (d, 1H, J=15.1 Hz), 3.20-3.80 (b, 8H), 4.29 (d, 1H, J=15.6 Hz), 4.90 (d, 1H, J=15.6 Hz), 5.04 (d, 1H, J=17.0 Hz), 5.09 (d, 1H, J=17.0 Hz), 5.37 (s, 1H), 5.99 (d, 1H, J=6.0 Hz), 7.20-7.85 (m, 18H).

IR (ν_{max}, KBr): 3430, 1640, 1450, 1408, 1228, 1113, 760, 700 cm^{-1}.

MS (EI) : 678 (M^+) :

The compounds shown in Tables 16 and 17 were similarly synthesized.

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Table 16

Compound No.	R^1	R^3	R^4	R^7	R^8	R^6	$R^{2'}$	Elementary analysis	Calcd. for (C, H, N) (%)	Found (C, H, N) (%)	MS(EI)
XIII-1	H	$(Ph)_2CH$	H	H	H	COOMe		$C_{34}H_{34}N_4O_5$	70.57, 5.92, 9.68	70.70, 5.88, 9.60	579(M^+)
XIII-2	H	$(Ph)_2CH$	H	Me	Me	COOMe		$C_{36}H_{38}N_4O_5$	71.27, 6.31, 9.23	71.43, 6.18, 9.21	607(M^+)
XIII-3	H	$(Ph)_2CH$	Me	H	H	NO_2		$C_{33}H_{33}N_5O_5$	68.38, 5.74, 12.08	68.51, 5.65, 11.98	580(M^+)
XIII-4	H	$(Ph)_2CH$	H	H	H	2-CN-Ph		$C_{39}H_{35}N_5O_3$	75.34, 5.67, 11.26	75.51, 5.59, 11.18	622(M^+)
XIII-5	H	$(Ph)_2CH$	H	H	H	2-(1-Tr-1H-tetrazol-5-yl)Ph		$C_{58}H_{50}N_8O_3$	76.80, 5.56, 12.35	76.96, 5.49, 12.24	907(M^+)
XIII-6	nPr	$(Ph)_2CH$	H	H	H	2-CN-Ph		$C_{42}H_{41}N_5O_3$	75.99, 6.23, 10.55	76.10, 6.19, 10.48	664(M^+)
XIII-7	iPr	$(Ph)_2CH$	H	H	H	2-CN-Ph		$C_{42}H_{41}N_5O_3$	75.99, 6.23, 10.55	76.15, 6.16, 10.48	664(M^+)
XIII-8	nBu	$(Ph)_2CH$	H	H	H	COOMe		$C_{38}H_{42}N_4O_5$	71.90, 6.67, 8.83	72.05, 6.58, 8.79	635(M^+)
XIII-9	nBu	$(Ph)_2CH$	Me	H	H	NO_2		$C_{37}H_{41}N_5O_5$	69.90, 6.50, 11.02	70.09, 6.44, 10.95	636(M^+)
XIII-10	nBu	$(Ph)_2CH$	H	H	H	2-CN-Ph		$C_{43}H_{43}N_5O_3$	76.19, 6.39, 10.33	76.31, 6.28, 10.21	678(M^+)
XIII-11	nBu	$(Ph)_2CH$	H	H	H	2-(1-Tr-1H-tetrazol-5-yl)Ph		$C_{62}H_{58}N_8O_3$	77.31, 6.07, 11.63	77.49, 5.95, 11.57	963(M^+)
XIII-12	nBu	$(Ph)_2CH$	H	H	H	2-CN-Ph		$C_{43}H_{43}N_5O_2S$	74.43, 6.25, 10.09	74.56, 6.21, 9.97	694(M^+)
XIII-13	nBu	$(Ph)_2CH$	H	H	H	2-CN-Ph		$C_{43}H_{44}N_6O_2$	76.30, 6.55, 12.42	76.48, 6.50, 12.23	677(M^+)

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Table 17

Compound No.	R^1	R^3	R^4	R^7	R^8	R^6	$R^{2'}$	Elementary analysis	Calcd. for (C, H, N) (%)	Found (C, H, N) (%)	MS(EI)
XIII-14	nBu	$(Ph)_2CH$	H	H	H	2-CN-Ph		$C_{42}H_{41}N_5O_2$	77.87, 6.38, 10.81	78.01, 6.29, 10.77	648(M^+)
XIII-15	nBu	$(Ph)_2CH$	H	H	H	2-CN-Ph		$C_{43}H_{43}N_5O_2$	78.03, 6.55, 10.58	78.18, 6.48, 10.52	662(M^+)
XIII-16	nBu	$(Ph)_2CH$	H	H	H	2-CN-Ph		$C_{44}H_{45}N_5O_2$	78.19, 6.71, 10.36	78.33, 6.64, 10.28	676(M^+)
XIII-17	nBu	$(Ph)_2CH$	H	H	H	2-CN-Ph	NH_2	$C_{39}H_{37}N_5O_2$	77.08, 6.14, 11.52	77.22, 6.05, 11.47	608(M^+)
XIII-18	nBu	$(Ph)_2CH$	H	H	H	2-CN-Ph	NHMe	$C_{40}H_{39}N_5O_2$	77.27, 6.32, 11.26	77.42, 6.28, 11.15	622(M^+)
XIII-19	nBu	$(Ph)_2CH$	H	H	H	2-CN-Ph	$N(Me)_2$	$C_{41}H_{41}N_5O_2$	77.45, 6.50, 11.02	77.61, 6.38, 10.95	636(M^+)
XIII-20	nBu	$(Ph)_2CH$	H	H	H	2-CN-Ph	$N(Et)_2$	$C_{43}H_{45}N_5O_2$	77.80, 6.83, 10.55	77.96, 6.74, 10.49	664(M^+)
XIII-21	nBu	(Ph)(c-Hex)CH	H	H	H	2-CN-Ph		$C_{43}H_{49}N_5O_3$	75.52, 7.22, 10.24	75.71, 7.14, 10.15	684(M^+)
XIII-22	nHex	$(Ph)_2CH$	H	H	H	2-CN-Ph		$C_{45}H_{47}N_5O_3$	76.57, 6.71, 9.92	76.71, 6.58, 9.86	706(M^+)

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Example 23: Process B, Step (j)

Synthesis of 4-[[(S)-2-n-butyl-1-[(4-carboxyphenyl)-methyl]5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-6-yl]carbonyl]morpholine (I-29)

The compound (XIII-8) (0.0761 g, 0.00012 mol) was dissolved in a 1/1 mixture of THF and MeOH (1.52 ml), followed by addition of a 1 N NaOH aqueous solution (0.38 ml), and the mixture was left as it was for 16.5 hours. The reaction mixture was concentrated, and a 1 N HCl aqueous solution (0.43 ml) (pH 4) was added thereto to cause acid precipitation. The resulting oily material was dissolved in $CHCl_3$, washed with water, dried over Na_2SO_4, and concentrated to obtain the objective compound (I-29) (0.0735 g; yield: 98.8%) as a white foamy material.

^{1}H-NMR ($CDCl_3$+D_2O) δ: 0.84 (t, 3H, J=7.3 Hz), 1.27 (sext, 2H, J=7.3 Hz), 1.57 (quint, 2H, J=7.3 Hz), 2.55 (t, 2H, J= 7.3 Hz), 2.70 (dd, 1H, J=6.0, 15.6 Hz), 2.86 (d, 1H, J=15.6 Hz), 3.30-3.65 (b, 8H), 4.24 (d, 1H, J=15.6 Hz), 5.06 (d, 1H, J=17.4 Hz), 5.10 (d, 1H, J=17.4 Hz), 5.12 (d, 1H, J=15.6 Hz), 5.43 (s, 1H), 5.97 (d, 1H, J=6.0 Hz), 7.12 (d, 2H, J= 8.3 Hz), 7.17-7.33 (m, 10H), 8.09 (d, 2H, J=8.3 Hz).

IR (ν_{max}, KBr) : 3460, 1715, 1646, 1453, 1412, 1270, 1230, 1115, 745, 700 cm^{-1}.

Example 24: Process B, Step (k)

Synthesis of 4-[[(S)-1-[(4-amino-3-methylphenyl)methyl]-5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-6-yl]carbonyl]morpholine (I'-1)

The compound (XIII-3) (1.0079 g, 0.00174 mol) was dissolved in 10 ml of ethyl acetate, then tin chloride dihydrate (1.9632 g, 0.00870 mol) was added thereto. The mixture was stirred on an 80°C oil bath in a stream of nitrogen for 30 minutes. The reaction mixture was cooled, neutralized with a 5% sodium carbonate aqueous solution, and concentrated. The residue was extracted with chloroform. The chloroform layer was washed with water, dried over anhydrous sodium sulfate, and concentrated to obtain a light-yellow foamy material. This substance was purified by silica gel column chromatography (chloroform/methanol = 70/1) to obtain the objective compound (I'-1) (0.8781 g; yield: 91.9%) as a white foamy material.

^{1}H-NMR ($CDCl_3$) δ: 2.10 (s, 3H), 2.74 (dd, 1H, J=6.4, 15.6 Hz), 3.20 (d, 1H, J=15.6 Hz), 3.2-3.8 (b, 10H), 4.29 (d, 1H, J=14.8 Hz), 4.75 (d, 1H, J=14.8 Hz), 4.80 (d, 1H, J=15.0 Hz), 4.90 (d, 1H, J=15.0 Hz), 5.35 (s, 1H), 6.01 (d, 1H, J=6.4 Hz), 6.62 (d, 1H, J=8.3 Hz), 6.80 (d, 1H, J=8.3 Hz), 6.81 (s, 1H), 7.1-7.4 (m, 11H) .

MS (EI) : 550 (M^+) .

Elementary analysis

Calcd. for $C_{33}H_{36}N_6O_3$ (%) : C, 72.11; H, 6.42; N, 12.74.

Found: C, 72.21; H, 6.35; N, 12.66.

Example 25: Process B, Step (l)

Synthesis of 4-[[(S)-2-n-butyl-5-diphenylacetyl-1-[(2'-1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-6-yl]carbonyl]morpholine (I-31)

Trimethyltin azide (0.0998 g, 0.000485 mol) was added to a solution of the compound (XIII-10) (0.1644 g, 0.000243 mol) in o-xylene (2.5 ml), and the mixture was stirred on a 120°C oil bath in a nitrogen stream for 90 hours. The reaction mixture was cooled. The insoluble portion was filtered out, washed with hot toluene, and vacuum dried. The resulting light-yellow solid was dissolved in MeOH (1.8 ml), and a 1 N HCl aqueous solution (0.9 ml) was added thereto, and the mixture was stirred at room temperature for 15 minutes. The reaction mixture was adjusted to pH 4 by adding a 1 N NaOH aqueous solution and then concentrated, and the residue was extracted with $CHCl_3$. The chloroform layer was washed with water, dried over anhydrous sodium sulfate, and concentrated to obtain a light-yellow foamy material. This material was purified by silica gel column chromatography (chloroform/methanol = 10/1) to obtain the objective compound (I-31) (0.1281 g; yield: 73.3%) as a white foamy material.

^{1}H-NMR ($CDCl_3$+D_2O) δ: 0.92 (t, 3H, J=7.3 Hz), 1.35 (sext, 2H, J=7.3 Hz), 1.52-1.73 (m, 2H), 1.38-2.75 (m, 4H), 3.20-3.67 (m, 8H), 3.76 (d, 1H, J=15.1 Hz), 4.54 (d, 1H, J=15.1 Hz), 4.92 (d, 1H, J=16.5 Hz), 5.05 (d, 1H, J=16.5 Hz), 5.14 (s, 1H), 5.81 (bs, 1H), 6.92-7.96 (m, 18H).

IR (ν_{max}, KBr): 3425, 1635, 1445, 1405, 1225, 1108, 748, 700 cm^{-1}.

MS (FAB) : 721 (M^+) .

Example 26: Process B, Step (m)

Synthesis of 4-[[(S)-5-diphenylacetyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-4,5,6,7-tetrahydro-

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1H-imidazo[4,5-c]pyridin-6-yl]carbonyl]morpholine (I-24)

A 12% HCl aqueous solution (5.5 ml) was added to a solution of the compound (XIII-5) (1.1103 g, 0.00122 mol) in THF (11 ml), and the mixture was stirred at room temperature for 4 hours. The reaction solution was neutralized by adding a 10% NaOH aqueous solution and concentrated. The residue was dissolved in a 1 N NaOH aqueous solution and the insoluble portion was filtered out. The filtrate was adjusted to pH 4 by adding a 1 N HCl aqueous solution and extracted with $CHCl_3$. The chloroform layer was washed with water, dried over anhydrous sodium sulfate, and concentrated to obtain a light-yellow foamy material. This material was purified by silica gel column chromatography (chloroform/methanol = 10/1) to obtain the objective compound (I-24) (0.7413 g; yield: 91.1%) as a white foamy material.

^{1}H-NMR (D_2O+NaOD) δ: 2.71 (dd, 1H, J=7.2 Hz), 2.80 (d, 1H, J=15.1 Hz), 3.2-3.8 (b, 8H), 4.27 (d, 1H, J=15.1 Hz), 5.85 (b, 1H), 6.8-8.1 (m, 19H).

MASS (FAB) : 665 (M^+)

Elementary analysis

Calcd. for $C_{39}H_{36}N_8O_3$ (%) : C, 70.46; H, 5.46; N, 16.86.

Found: C, 70.55; H, 5.40; N, 16.71.

Example 27: Process B, Step (n)

Synthesis of 4-[[(S)-1-[[4-(2-carboxybenzamido)-3-methyl]phenyl]methyl]-5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-6-yl]carbonyl]-morpholine (I-23)

A solution of phthalic anhydride (0.3236 g, 0.00219 mol) in ethyl acetate (3.3 ml) was added to a solution of the compound (I'-1) (0.8007 g, 0.00146 mol) in ethyl acetate (12 ml) with stirring at room temperature, and the mixture was stirred for 23 hours. The reaction mixture was filtered, and the resulting white solid was washed with ethyl acetate and dried to obtain the objective compound (I-23) (0.8691 g; m.p. 191-196°C ; yield: 85.5%).

^{1}H-NMR (D_2O+NaOD) δ: 2.24 (s, 3H), 2.30, 2.75 (each dd, 1H, J=5.6, 16.1 Hz), 2.95, 3.11 (each, d, 1H, J=16.1 Hz), 3.2-3.8 (b, 8H), 3.9-4.1 (m, 1H), 5.70 (b, 1H), 6.9-8.0 (m, 17H), 9.7 (b, 1H).

MASS (FAB) : 698 (M^+).

Elementary analysis

Calcd. for $C_{41}H_{39}N_5O_6$ (%) : C, 70.57; H, 5.63; N, 10.04.

Found: C, 70.79; H, 5.48; N, 10.01.

The compounds shown in Tables 18 and 19 were synthesized in the similar way.

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Table 18

Compound No.	R^1	R^2	R^3	R^4	R	R^7	R^8	Elementary analysis	Calcd. for (C, H, N) (%)	Found (C, H, N) (%)	MS(FAB)
I-21	H		$(Ph)_2CH$	H	COOH	H	H	$C_{33}H_{32}N_4O_5$	70.20, 5.71, 9.92	70.39, 5.65, 9.88	565, M^+
I-22	H		$(Ph)_2CH$	H	COOH	Me	Me	$C_{35}H_{36}N_4O_5$	70.93, 6.12, 9.45	80.05, 6.08, 9.40	593, M^+
I-23	H		$(Ph)_2CH$	Me	NHCO(2-COOH-Ph)	H	H	$C_{41}H_{39}N_5O_6$	70.57, 5.63, 10.04	70.79, 5.48, 10.01	698, M^+
I-24	H		$(Ph)_2CH$	H	2-(1H-tetrazol-5-yl)Ph	H	H	$C_{39}H_{36}N_8O_3$	70.46, 5.46, 16.86	70.55, 5.40, 16.71	665, M^+
I-25	nPr		$(Ph)_2CH$	H	2-(1H-tetrazol-5-yl)Ph	H	H	$C_{42}H_{42}N_8O_3$	71.37, 5.99, 15.85	71.50, 5.92, 15.79	707, M^+
I-26	iPr		$(Ph)_2CH$	H	2-(1H-tetrazol-5-yl)Ph	H	H	$C_{42}H_{42}N_8O_3$	71.37, 5.99, 15.85	71.46, 5.98, 15.81	707, M^+
I-27	nBu	CH_2OH	$(Ph)_2CH$	H	COOH	H	H	$C_{33}H_{35}N_3O_4$	73.72, 6.56, 7.82	73.91, 6.49, 7.80	538, M^+
I-28	nBu	COOH	$(Ph)_2CH$	H	COOH	H	H	$C_{33}H_{33}N_3O_5$	71.85, 6.03, 7.62	72.01, 5.98, 7.56	552, M^+
I-29	nBu		$(Ph)_2CH$	H	COOH	H	H	$C_{37}H_{40}N_4O_5$	71.59, 6.49, 9.03	71.66, 6.39, 8.99	621, M^+
I-30	nBu		$(Ph)_2CH$	Me	NHCO(2-COOH-Ph)	H	H	$C_{45}H_{47}N_5O_6$	71.69, 6.28, 9.29	71.77, 6.20, 9.25	754, M^+
I-31	nBu		$(Ph)_2CH$	H	2-(1H-tetrazol-5-yl)Ph	H	H	$C_{43}H_{44}N_8O_3$	71.65, 6.15, 15.54	71.79, 6.10, 15.49	721, M^+
I-32	nBu		$(Ph)_2CH$	H	2-(1H-tetrazol-5-yl)Ph	H	H	$C_{43}H_{44}N_8O_2S$	70.08, 6.02, 15.21	70.20, 5.98, 15.16	737, M^+

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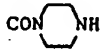
Table 19

Compound No.	R^1	R^2	R^3	R^4	R	R^7	R^8	Elementary analysis	Calcd. for (C, H, N) (%)	Found (C, H, N) (%)	MS(FAB)
I-33	nBu		$(Ph)_2CH$	H	2-(1H-tetrazol-5-yl)Ph	H	H	$C_{43}H_{45}N_9O_2$	71.74, 6.30, 17.51	71.89, 6.18, 17.49	720, M^+
I-34	nBu		$(Ph)_2CH$	H	2-(1H-tetrazol-5-yl)Ph	H	H	$C_{42}H_{42}N_8O_2$	73.02, 6.13, 16.22	73.18, 6.09, 16.17	691, M^+
I-35	nBu		$(Ph)_2CH$	H	2-(1H-tetrazol-5-yl)Ph	H	H	$C_{43}H_{44}N_8O_2$	73.27, 6.29, 15.90	73.45, 6.18, 15.88	705, M^+
I-36	nBu		$(Ph)_2CH$	H	2-(1H-tetrazol-5-yl)Ph	H	H	$C_{44}H_{46}N_8O_2$	73.51, 6.45, 15.59	73.51, 6.45, 15.59	719, M^+
I-37	nBu	$CONH_2$	$(Ph)_2CH$	H	2-(1H-tetrazol-5-yl)Ph	H	H	$C_{39}H_{38}N_8O_2$	71.98, 5.89, 17.22	72.10, 5.76, 17.19	651, M^+
I-38	nBu	CONHMe	$(Ph)_2CH$	H	2-(1H-tetrazol-5-yl)Ph	H	H	$C_{40}H_{40}N_8O_2$	72.27, 6.06, 16.86	72.49, 5.98, 16.79	665, M^+
I-39	nBu	$CON(Me)_2$	$(Ph)_2CH$	H	2-(1H-tetrazol-5-yl)Ph	H	H	$C_{41}H_{42}N_8O_2$	72.54, 6.24, 16.51	72.70, 6.18, 16.47	679, M^+
I-40	nBu	$CON(Et)_2$	$(Ph)_2CH$	H	2-(1H-tetrazol-5-yl)Ph	H	H	$C_{43}H_{46}N_8O_2$	73.06, 6.56, 15.85	73.21, 6.48, 15.80	707, M^+
I-41	nBu		(Ph)(c-Hex)CH	H	2-(1H-tetrazol-5-yl)Ph	H	H	$C_{43}H_{50}N_8O_3$	71.05, 6.93, 15.41	71.19, 6.90, 15.37	727, M^+
I-42	nHex		$(Ph)_2CH$	H	2-(1H-tetrazol-5-yl)Ph	H	H	$C_{45}H_{46}N_8O_3$	72.36, 6.21, 15.00	72.33, 6.39, 14.88	747, M^+

There were also similarly synthesized the compounds shown in Table 20.

Table 20

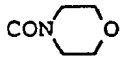
Compound No.	R^1	R^2	R^3	R^4	R^7	R^8	R^{10}	MS(EI)
I'-1	H		$(Ph)_2CH$	Me	H	H	NH_2	550(M^+)
I'-2	nBu		$(Ph)_2CH$	Me	H	H	NH_2	606(M^+)

Table 20 (continued)

Compound No.	Elementary analysis	Calcd. for (C, H, N) (%)	Found (C, H, N) (%)

Example 29: Process B, Step (p)

Synthesis of (S)-3-(2-n-butyl-1-triphenylmethyl-imidazol-5-yl)-2-(triphenylmethylamino)propanoic acid (XXV-3)

PDC (0.7845 g, 0.00208 mol) was added to a solution of the compound (XXIV-3) (0.4063 g, 0.000596 mol) in DMF (4.0 ml) and stirred at room temperature for 8 hours. The reaction mixture was poured into water and extracted with CH_2Cl_2. The organic layer was washed with water and then with a saturated NaCl aqueous solution, dried over Na_2SO_4, and concentrated to obtain a reddish brown oily product (0.5745 g, 100% up). This product was purified by silica gel column chromatography (hexane/acetone = 2/1 → 1/2 and $CHCl_3$/MeOH = 30/1) to obtain the objective compound (XXV-3) (0.1256 g; yield: 39.3%) as a light-yellow oily material.

^{1}H-NMR ($CDCl_3$) δ: 0.59 (t, 3H, J=7.3 Hz), 0.91 (sext, 2H, J=7.3 Hz), 1.16 (quint, 2H, J=7.3 Hz), 1.68-1.79 (m, 3H), 2.31 (dd, 1H, J=9.1, 15.3 Hz), 3.53 (d, 1H, J=9.1 Hz), 5.93 (s, 1H), 7.04-7.45 (m, 30H).

IR (ν_{max}, KBr): 3025, 2980, 1715, 1608, 1510, 1460, 1410, 1390, 1370, 1190, 1158, 910, 730, 703 cm^{-1}.

The compounds shown in Table 22 were synthesized in the similar way.

Table 22

Compound No.	R^1	Elementary analysis	Calcd. for (C, H, N) (%)			Found (C, H, N) (%)			MS(FAB)
XXV-1	nPr	$C_{47}H_{43}N_3O_2$	82.79,	6.36,	6.16	82.93,	6.27,	6.03	682(M^+)
XXV-2	iPr	$C_{47}H_{43}N_3O_2$	82.79,	6.36,	6.16	82.88,	6.29,	6.08	682(M^+)
XXV-3	nBu	$C_{48}H_{45}N_3O_2$	82.85,	6.52,	6.04	83.01,	6.44,	5.95	696(M^+)
XXV-4	nHex	$C_{50}H_{49}N_3O_2$	82.95,	6.82,	5.80	83.11,	6.74,	5.68	724(M^+)

Example 30: Process B, Step (q)

Synthesis of (S)-2-amino-3-(2-n-butyl-1H-imidazol-5-yl)propanoic acid (XXV'-3) and (S)-2-n-butyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylic acid hydrochloride (XXVI-3)

A 1 N HCl aqueous solution (3.3 ml) and a 37% HCHO solution (0.2 ml) were added to the compound (XXV-3) (0.3308 g, 0.000475 mol) and stirred at room temperature for 40 minutes and then in a 120°C oil bath for 4 hours. After the reaction mixture was cooled, the insoluble portion was filtered out and washed with water. The aqueous layer was washed with Et_2O, then concentrated, and dried to obtain the objective compound (XXVI-3) (0.1401 g; yield: 99.5%) as a yellow viscous material.

^{1}H-NMR (D_2O+NaOD) δ: 0.95 (t, 3H, J=7.3 Hz), 1.40 (sext, 2H, J=7.3 Hz), 1.80 (quint, 2H, J=7.3 Hz), 3.03 (t, 2H, J=7.3 Hz), 3.0-3.4 (m, 2H), 3.8-4.3 (m, 2H) .

MS (FAB) : 223 (M-2HCl)

The compounds shown in Table 23 were similarly synthesized.

Table 23

Compound No.	R^1	MS (FAB)
XXVI-1	nPr	209(M-2HCl)
XXVI-2	iPr	209(M-2HCl)
XXVI-3	nBu	223(M-2HCl)
XXVI-4	nHex	251(M-2HCl)

By using the compound (XXV-3) (0.3001 g, 0.000431 mol) and a 1 N HCl aqueous solution (3.0 ml), the above reaction procedure was repeated without adding the 37% HCHO solution to obtain the compound (XXV'-3) (0.1225 g; yield: 100%) as a yellow viscous material.

^{1}H-NMR (D_2O+NaOD) δ: 0.96 (t, 3H, J=7.3Hz), 1.39 (sext, 2H, J=7.3Hz), 1.82 (quint, 2H, J=7.3Hz), 2.5-

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3.7 (m, 3H), 3.07 (t, 2H, J=7.3Hz), 6.85 (bs, 1H).

MASS (FAB) : 211 (M-2HCl)

There were similarly synthesized the compounds shown in Table 24.

Table 24

Compound No.	R^1	MS (FAB)
XXV'-1	nPr	197 (M-2HCl)
XXV'-2	iPr	197 (M-2HCl)
XXV'-3	nBu	211 (M-2HCl)
XXV'-4	nHex	239 (M-2HCl)

Example 31: Process B, Step (r)

Synthesis of (S)-2-n-butyl-5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylic acid (XXVII-3)

Diphenylacetic acid (0.3114 g, 0.00147 mol), DCCI (0.3027 g, 0.00147 mol), and HBTA (0.1983 g, 0.00147 mol) were dissolved in dry THF (0.8 ml) and stirred at room temperature for 20 minutes. A solution of the compound (XXVI-3) (0.1358 g, 0.000458 mol) in dry THF (2.7 ml), and dry triethylamine (0.13 ml, 0.000963 mol) were added to this mixture, followed by stirring at room temperature for 16 hours. The insoluble portion was filtered out and washed with THF. The filtrate and washings were joined and concentrated to obtain a crude oily product (0.3065 g). This product was dissolved in a 1/1 mixture of THF and MeOH (6.0 ml) and, after addition of a 1 N HCl aqueous solution (2.0 ml), left as it was for 8 hours. Further a 1/1 mixture of THF and MeOH (6.0 ml) and a 1 N NaOH aqueous solution (4.0 ml) were added, and the mixture was left as it was for 8 hours. The reaction mixture was concentrated and the residue was purified by silica gel column chromatography (chloroform/ methanol = 10/1) to obtain the objective compound (XXVII-3) (0.0829 g; yield: 43.3%) as a white foamy material.

^{1}H-NMR (D_2O+NaOD) δ: 0.92 (t, 3H, J=7.2 Hz), 1.39 (sext, 2H, J=7.2 Hz), 1.82 (quint, 2H, J=7.2 Hz), 2.3-2.9 (m, 4H), 3.9-4.8 (m, 2H), 5.51 (s, 1H), 5.73 (bs, 1H), 7.1-7.7 (m, 10H) .

MASS (FAB) : 417 (M^+)

Elementary analysis

Calcd. for $C_{25}H_{27}N_3O_3$ (%) : C, 71.92; H, 6.52; N, 10.06.

Found: C, 72.08; H, 6.47; N, 9.99.

The compounds shown in Table 25 were similarly synthesized.

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Table 25

Compound No.	R^1	R^3	Elementary analysis	Calcd. for (C, H, N) (%)	Found (C, H, N) (%)	MS(FAB)
XXVII-1	nPr	$(Ph)_2CH$	$C_{24}H_{25}N_3O_3$	71.44, 6.25, 10.41	71.61, 6.17, 10.35	403(M^+)
XXVII-2	iPr	$(Ph)_2CH$	$C_{24}H_{25}N_3O_3$	71.44, 6.25, 10.41	71.59, 6.19, 10.37	403(M^+)
XXVII-3	nBu	$(Ph)_2CH$	$C_{25}H_{27}N_3O_3$	71.92, 6.52, 10.06	80.07, 6.48, 9.98	417(M^+)
XXVII-4	nHex	$(Ph)_2CH$	$C_{27}H_{31}N_3O_3$	72.78, 7.01, 9.43	72.91, 6.94, 9.35	446(M^+)
XXVII-5	nBu	(Ph)(c-Hex)CH	$C_{25}H_{33}N_3O_3$	70.89, 7.85, 9.92	71.01, 7.78, 9.85	424(M^+)

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Example 32: Process B, Step (s)

Synthesis of (S)-2-n-butyl-1-[(4-methoxycarbonylphenyl)methyl]-5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo-[4,5-c]pyridine-6-carboxylic acid (XIV-8)

Methyl 4-(bromomethyl)benzoate (0.0521 g, 0.000227 mol) and K_2CO_3 (0.0314 g, 0.000227 mol) were added to a solution of the compound (XXVII-3) (0.0791 g, 0.000189 mol) in dry DMF (1.6 ml), and the mixture was stirred vigorously at room temperature for 20 hours. The reaction mixture was poured into water, extracted with EtOAc, washed with water, dried over anhydrous sodium sulfate, and concentrated to obtain a light-yellow oily material. This material was purified by silica gel column chromatography (hexane/acetone = 1/2) to obtain the objective compound (XIV-8) (0.0331g; m.p. 176-180°C), its 3-position isomer (0.0382 g) and a mixture of them (0.0018 g; yield: 68.2%) as colorless crystals.

MASS (FAB) : 566 (M^+)

Elementary analysis

Calcd. for $C_{34}H_{36}N_3O_5$ (%) : C, 72.19; H, 6.24; N, 7.43.

Found: C, 72.30; H, 6.21; N, 7.39.

Example 33

Receptor binding test

Determination of total binding in the presence of each drug to be tested was made in the following way. A test drug of a predetermined concentration (0.025 ml; dissolved in dimethyl sulfoxide, then diluted two-fold with a buffer attached to the Drug Discovery System and used for assay), a tracer (0.025 ml), and a receptor (0.2 ml) were added to make a total volume of 0.25 ml. After incubation (at room temperature for 3 hours for the angiotensin II receptor type 1 (AT_1) and at 37°C for one hour for the type 2 (AT_2)), the reaction mixture was subjected to suction filtration (using GF/C filter paper for AT_1 and GF/B filter paper for AT_2). The filter paper (tracer-receptor complex) after suction filtration was measured by a γ-well counter (ARC-500, Aloka). The non-specific binding was determined by the similar operation by using a large excess of displacer. The specific binding at the predetermined concentration of the test drug was calculated by deducting the non-specific binding from the total binding.

The ratio (%) at which the test drugs inhibit binding between radioactive ligand and receptor was determined for both AT_1 and AT_2 by using the test drugs of the predetermined concentration and a control drug.

The compound of the present invention competes with both of the angiotensin II receptors AT_1 and AT_2, but it is noted that the compound of the formula (I) wherein R_1 is H competes specifically with AT_2 and that of the formula (I) wherein R_1 is other than H competes specifically with AT_1.

In USP 5,091,390, it is stated that the compounds claimed therein, including some reference compounds described below, compete selectively with AT_2 regardless of R^1, but the present inventors found that the compound of the present invention and the reference compounds compete specifically with one of AT_1 and AT_2 receptors according to the difference of R^1, and that the activity of the compound of the present invention far excels that of the reference compounds.

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Table 26: Binding inhibition ratio (%) of the test compounds at 1 μM

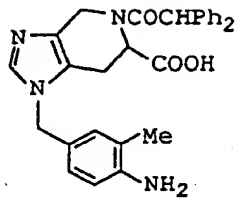
Test compound	AT_1*	AT_2**
Compound I-1	0	100
Compound I-2	0	100
Compound I-7	0	100
Compound I-12	100	0
Compound I-17	100	0
Compound I-19	100	0
Compound I-21	0	100
Compound I-23	0	100
Compound I-24	0	100
Compound I-30	100	0
Compound I-31	100	0
Compound I-32	100	0
Compound I-40	100	0
Reference compound PD123177	0	65
Reference compound DuP753	70	0
Reference compound 1	0	71
Reference compound 2	0	72
Reference compound 26	78	0
Reference compound 27	0	76
Reference compound 50	75	0

* Receptor: suprarenal gland of rabbit
Tracer: ^{3}H-angiotensin II (displacer: DuP753)

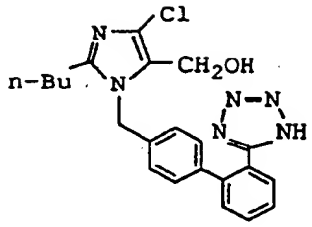
** Receptor: bovine cerebellar cortex
Tracer: ^{125}I-Tyr^{4}-angiotensin II (displacer: angiotensin II (human))

PD123177 and DuP753 are disclosed in Bioorganic & Medical Chemistry Letters, 1(12), 711-716, 1991.

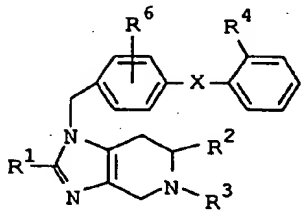
PD123177



DuP753



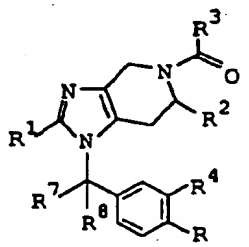
Comparative substances 1, 2, 26, 27 and 50 are the compounds disclosed in USP 5,091,390:



Reference compound	R^1	R^2	R^3	X	R^4	R^6
1	H	COOH	$COCH(Ph)_2$	NHCO	COOH	3-CH_3
2	H	$COOCH_3$	$COCH(Ph)_2$	NHCO	COOH	3-CH_3
26	C_3H_7	COOH	$COCH(Ph)_2$	single bond	tetrazolyl	3-CH_3
27	H	COOH	$COCH(Ph)_2$	single bond	tetrazolyl	H
50	C_3H_7	COOH	$COCH(Ph)_2$	single bond	tetrazolyl	H

Claims

1. A compound of formula (I) :



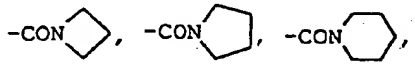
(I)

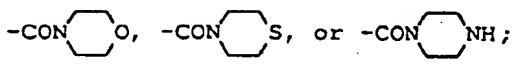
or a pharmaceutically acceptable salt thereof; wherein

R^1 represents
hydrogen,
halogen,
C_1-C_6 alkyl,
C_3-C_6 alkenyl,
C_3-C_6 alkynyl,

	$R^{20}(CH_2)_n$- wherein R^{20} represents C_3-C_8 cycloalkyl, naphthyl, phenyl, or phenyl substituted with one to five of C_1-C_4 alkyl, halogen atom, trifluoromethyl, hydroxy, C_1-C_4 alkoxy, C_1-C_3 acyloxy, amino, N-mono- C_1-C_4 alkylamino, N-di-C_1-C_4 alkylamino, C_1-C_4 thioalkyl, C_1-C_3 alkylsulfonyl, nitro, and -$NHCOR^{21}$ wherein R^{21} represents C_1-C_3 alkyl, phenyl, C_1-C_3 alkylphenyl, aminophenyl, or C_1-C_4 alkylaminophenyl, and n is an integer of 1 to 6, R^{20}-C(O)- wherein R^{20} is as defined above, or R^{20}-CH(OH)- wherein R^{20} is as defined above;
R^2	represents carbamoyl, mono- or di-C_1-C_6 alkylcarbamoyl, or 4- to 6-membered heterocyclic carbamoyl;
R	represents amino, carboxy, (1H-tetrazol-5-yl)phenyl, carboxyphenyl, carboxybenzamido, (1H-tetrazol-5-yl)benzamido, carboxyphenylcarbamoyl, or (1H-tetrazol-5-yl)-phenylcarbamoyl;
R^3	represents -CH_2(phenyl), -CH(phenyl)$_2$, -CH(phenyl)CH_3, -CH(phenyl) (cyclohexyl), -CH_2CH_2(phenyl), -CH_2(C_1-C_6 alkoxyphenyl), or -CH_2(hydroxyphenyl); and
R^4, R^7, and R^8	each independently represents hydrogen or C_1-C_6 alkyl.

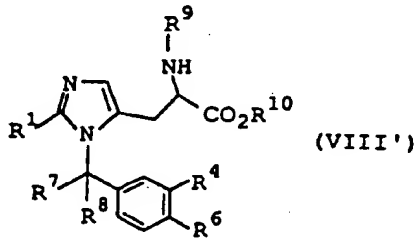
2. A compound or a pharmaceutically acceptable salt thereof according to claim 1, wherein R^1 is hydrogen or C_1-C_6 alkyl; R^2 is -$CONH_2$, -$CONHCH_3$, -$CON(CH_3)_2$, -$CONH(C_2H_5)$, -$CON(C_2H_5)_2$,





R is amino, carboxy, 2-(1H-tetrazol-5-yl)phenyl, 2-carboxyphenyl, 2-carboxybenzamido, 2-(1H-tetrazol-5-yl)benzamido, 2-carboxyphenylcarbamoyl, or 2-(1H-tetrazol-5-yl)phenylcarbamoyl; R^3 is -CH(phenyl)$_2$, -CH_2(phenyl), -CH(phenyl)CH_3, -CH(phenyl) (cyclohexyl), -CH_2CH_2(phenyl), -CH_2(p-methoxyphenyl), or -CH_2(p-hydroxyphenyl); and R^4, R^7, and R^8 each independently is hydrogen or C_1-C_2 alkyl.

3. A compound of formula (VIII') :



(VIII')

or a salt thereof; wherein
R^1, R^4, R^7 and R^8 are as defined in claim 1 or 2;
R^6 is nitro, (1-triphenylmethyl-1H-tetrazol-5-yl)phenyl, cyano, C_1-C_3 alkoxycarbonyl, or cyanophenyl;
R^9 is hydrogen or t-butoxycarbonyl; and
R^{10} is hydrogen or C_1-C_6 alkyl.

4. A compound or a salt thereof according to claim 3, wherein R^1 is hydrogen or C_1-C_6 alkyl; R^4 is hydrogen or C_1-C_2 alkyl; R^6 is nitro, 2-(1-trifluoromethyl-1H-tetrazol-5-yl)phenyl, or 2-cyanophenyl; R^7 and R^8 each independently is hydrogen or C_1-C_6 alkyl; and R^{10} is hydrogen or C_1-C_6 alkyl.

5. A compound of formula (XXVIII) :

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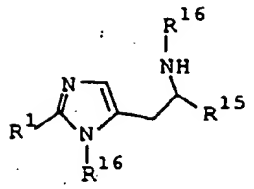
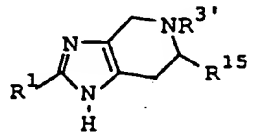


(XXVIII)

or a salt thereof; wherein
R^1 is as defined in claim 1 or 2;
R^{15} represents $-CH_2-R^{17}$ or $-C(O)-R^{17}$ wherein R^{17} represents hydroxy or t-butyldimethylsilyloxy; and
R^{16} represents hydrogen or triphenylmethyl;
with provisos that when R^1 and R^{16} are both hydrogen, R^{15} is not $-CH_2-OH$, and that when R^1 is hydrogen or methyl and R^{16} is hydrogen, R^{15} is not -COOH.

6. A compound of formula (XXIX) :

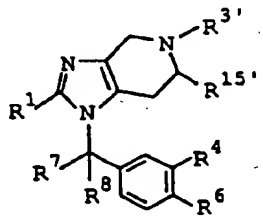


(XXIX)

or a salt thereof; wherein
R^1 is as defined in claim 1 or 2;
R^{15} represents $-CH_2-R^{17}$ or $-C(O)-R^{17}$ wherein R^{17} represents hydroxy or t-butyldimethylsilyloxy; and
$R^{3'}$ represents hydrogen, $-COCH_2(phenyl)$, $-COCH(phenyl)_2$, $-COCH(phenyl)CH_3$, -COCH(phenyl) (cyclohexyl), $-COCH_2CH_2(phenyl)$, $-COCH_2(C_1-C_6$ alkoxyphenyl), or $-COCH_2$(hydroxyphenyl);
with proviso that when R^1 and $R^{3'}$ are both hydrogen, R^{15} is not -COOH.

7. A compound or a salt thereof according to claim 6, wherein R^1 is hydrogen or C_1-C_6 alkyl; R^{15} is -COOH; and $R^{3'}$ is $-COCH(phenyl)_2$ or -COCH(phenyl) (cyclohexyl) .

8. A compound of formula (XXX) :



(XXX)

or a salt thereof; wherein
R^1, R^4, R^7 and R^8 are as defined in claim 1 or 2;
$R^{3'}$ is as defined in claim 6;
R^6 is as defined in claim 3 or 4; and
$R^{15'}$ represents $-CH_2-R^{19}$ or $-C(O)-R^{19}$ wherein R^{19} represents hydrogen or C_1-C_6 alkyl.

9. A compound or a salt thereof according to claim 8, wherein R^1 is hydrogen or C_1-C_6 alkyl; $R^{3'}$ is $-COCH(phenyl)_2$ or -COCH(phenyl) (cyclohexyl); R^6 is nitro, 2-(1-triphenylmethyl-1H-tetrazol-5-yl)phenyl, cyano, methoxycarbonyl, or 2-cyanophenyl; R^4, R^7, and R^8 each independently is hydrogen or C_1-C_2 alkyl; and R^{19} is hydrogen or C_1-C_2 alkyl.

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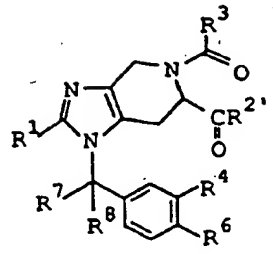
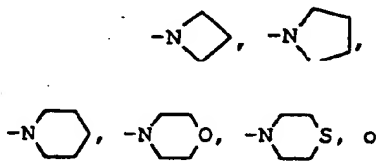
10. A compound of formula (XIII) :



(XIII)

or a salt thereof; wherein
R^1, R^3, R^4, R^7 and R^8 are as defined in claim 1 or 2;
R^6 is as defined in claim 3 or 4; and
$R^{2'}$ represents amino, mono or di-C_1-C_6 alkylamino, or 4- to 6- membered heterocyclic amino.

11. A compound or a salt thereof according to claim 10, wherein R^1 is hydrogen or C_1-C_6 alkyl; R^2 is $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NH(C_2H_5)$, $N(C_2H_5)_2$,



R^3 is $-CH(phenyl)_2$, or -CH(phenyl) (cyclohexyl); R^4, R^7, and R^8 each independently is hydrogen or C_1-C_2 alkyl; and R^6 is nitro, 2-(1-triphenylmethyl-1H-tetrazol-5-yl)phenyl, methoxycarbonyl, cyano, or 2-cyanophenyl.

12. A compound of formula (I) or a pharmaceutically acceptable salt thereof as defined in claim 1 or 2 for use in a method of treatment of the human or animal body by therapy.

13. A compound of formula (I) or a pharmaceutically acceptable salt thereof as defined in claim 1 or 2 for use as an angiotensin II antagonist.

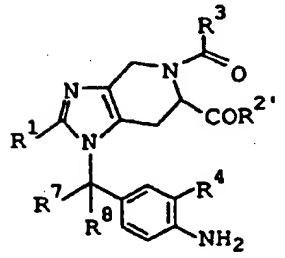
14. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined in claim 1 or 2 in the manufacture of a medicament for use as an angiotensin II antagonist.

15. An angiotensin II antagonist composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined in claim 1 and a pharmaceutically acceptable diluent.

16. A compound of formula (I) or a pharmaceutically acceptable salt thereof as defined in claim 1 or 2 with the proviso that R^1 is not hydrogen for use as an angiotensin II AT_1 receptor antagonist.

17. A compound of formula (I) or a pharmaceutically acceptable salt thereof as defined in claim 1 or 2 wherein R^1 is hydrogen for use as an angiotensin II AT_2 receptor antagonist.

18. A process for preparing a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined in claim 1 or 2, which comprises:
(i) reacting a compound of formula (II) :

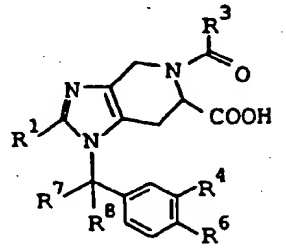


(II)

wherein R^1, R^3, R^4, R^7 and R^8 are as defined in claim 1 and $R^{2'}$ is amino, mono- or di-C_1-C_6 alkylamino, or 4- to 6- membered heterocyclic amino, or a salt thereof, with an appropriate benzonic acid derivative at 10 to 40°C for 10 to 24 hours;

(ii) hydrolysing a compound of formula (XIII) or a salt thereof as defined in claim 10 wherein R^6 is cyanophenyl;

(iii) reacting a compound of formula (IV) :



(IV)

wherein R^1, R^3, R^4, R^7 and R^8 are as defined in claim 1 and R^6 is (1H-tetrazol-5-yl)phenyl or a salt thereof with an appropriate nitrogen-containing compound at 10 to 40°C for 10 to 24 hours;

(iv) reacting a compound of formula (XIII) or a salt thereof as defined in claim 10 wherein R^6 is C_1-C_3 alkoxycarbonyl with an alkali at 10 to 40°C for 1 to 24 hours;

(v) reacting a compound of formula (XIII) or a salt thereof as defined in claim 10 wherein R^6 is nitro with tin chloride or tin chloride dihydrate under an inert gas atmosphere at 10 to 100°C for 0.1 to 1 hour;

(vi) reacting a compound of formula (XIII) or a salt thereof as defined in claim 10 wherein R^6 is cyanophenyl with trimethyltin azide or tributyltin azide under an inert gas atmosphere at 100 to 120°C for 12 to 120 hours followed by treatment with an acid; or

(vii) reacting a compound of formula (XIII) or a salt thereof as defined in claim 10 wherein R^6 is ((1-triphenylmethyl)-1H-tetrazol-5-yl)phenyl with an acid at 10 to 100°C for 0.1 to 6 hours;

and, if desired, converting a compound of formula (I) into another compound of formula (I), and/or, if desired, converting a compound of formula (I) into a pharmaceutically acceptable salt thereof, and/or, if desired, converting a salt into a free compound.

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